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(74) Agents: **MILOWSKY, Arnold, S.**; Wyeth, Patent Law
Department, Five Giralda Farms, Madison, NJ 07940-0874
et al. (US).

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(71) Applicant: **WYETH** [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: **MEWSHAW, Richard, Eric**; 251 West DeKalb Pike, Apartment B509, King of Prussia, PA 19406 (US). **EDSALL, Richard, James**; 33308 Glenwood Avenue, Quakertown, PA 18951 (US). **COHN, Stephen, Todd**; 2 Ptarmigan Drive, Reading, PA 19606 (US). **HARRIS, Heather, Anne**; 210 Pine Drive, Phoenixville, PA 19460 (US). **KEITH, James, Carl, Jr.**; 28 Vine Street, Andover, MA 01810 (US). **ALBERT, Leo, Massillamoney**; 17 Freeport Drive, Burlington, MA 01803 (US).

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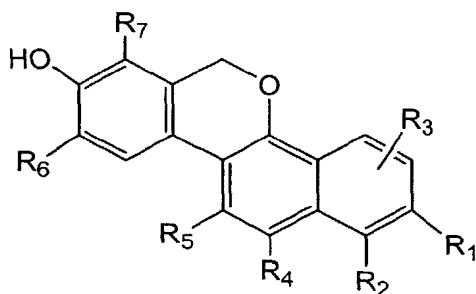
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(54) Title: SUBSTITUTED 6H-DIBENZO[c,h]CHROMENES AS ESTROGENIC AGENTS



(I)

(57) Abstract: This invention provides estrogen receptor modulators of formula (I), having the structure, wherein R₁, R₂, R₃, R₄, R₅, R₆, and R₇ are as defined in the specification, or a pharmaceutically acceptable salt thereof.

WO 03/051863 A1

SUBSTITUTED 6H-DIBENZO[c,h]CHROMENES AS ESTROGENIC AGENTS**BACKGROUND OF THE INVENTION**

5 This invention relates to substituted 6H-dibenzo[c,h]chromenes, which are useful as estrogenic agents.

The pleiotropic effects of estrogens in mammalian tissues have been well documented, and it is now appreciated that estrogens affect many organ systems [Mendelsohn and Karas, New England Journal of Medicine 340: 1801-1811 (1999), Epperson, et al., Psychosomatic Medicine 61: 676-697 (1999), Crandall, Journal of
10 Womens Health & Gender Based Medicine 8: 1155-1166 (1999), Monk and Brodaty, Dementia & Geriatric Cognitive Disorders 11: 1-10 (2000), Hurn and Macrae, Journal of Cerebral Blood Flow & Metabolism 20: 631-652 (2000), Calvin, Maturitas 34: 195-210 (2000), Finking, et al., Zeitschrift fur Kardiologie 89: 442-453 (2000), Brincat, Maturitas 35: 107-117 (2000), Al-Azzawi, Postgraduate Medical Journal 77: 292-304
15 (2001)]. Estrogens can exert effects on tissues in several ways, and the most well characterized mechanism of action is their interaction with estrogen receptors leading to alterations in gene transcription. Estrogen receptors are ligand-activated transcription factors and belong to the nuclear hormone receptor superfamily. Other members of this family include the progesterone, androgen, glucocorticoid and
20 mineralocorticoid receptors. Upon binding ligand, these receptors dimerize and can activate gene transcription either by directly binding to specific sequences on DNA (known as response elements) or by interacting with other transcription factors (such as AP1), which in turn bind directly to specific DNA sequences [Moggs and Orphanides, EMBO Reports 2: 775-781 (2001), Hall, et al., Journal of Biological
25 Chemistry 276: 36869-36872 (2001), McDonnell, Principles Of Molecular Regulation. p351-361(2000)]. A class of "coregulatory" proteins can also interact with the ligand-bound receptor and further modulate its transcriptional activity [McKenna, et al., Endocrine Reviews 20: 321-344 (1999)]. It has also been shown that estrogen receptors can suppress NFκB-mediated transcription in both a ligand-dependent and
30 independent manner [Quaedackers, et al., Endocrinology 142: 1156-1166 (2001), Bhat, et al., Journal of Steroid Biochemistry & Molecular Biology 67: 233-240 (1998), Pelzer, et al., Biochemical & Biophysical Research Communications 286: 1153-7 (2001)].

Estrogen receptors can also be activated by phosphorylation. This phosphorylation is mediated by growth factors such as EGF and causes changes in gene transcription in the absence of ligand [Moggs and Orphanides, EMBO Reports 2: 775-781 (2001), Hall, et al., Journal of Biological Chemistry 276: 36869-36872 (2001)].

A less well-characterized means by which estrogens can affect cells is through a so-called membrane receptor. The existence of such a receptor is controversial, but it has been well documented that estrogens can elicit very rapid non-genomic responses from cells. The molecular entity responsible for transducing these effects has not been definitively isolated, but there is evidence to suggest it is at least related to the nuclear forms of the estrogen receptors [Levin, Journal of Applied Physiology 91: 1860-1867 (2001), Levin, Trends in Endocrinology & Metabolism 10: 374-377 (1999)].

Two estrogen receptors have been discovered to date. The first estrogen receptor was cloned about 15 years ago and is now referred to as ER α [Green, et al., Nature 320: 134-9 (1986)]. The second form of the estrogen receptor was found comparatively recently and is called ER β [Kuiper, et al., Proceedings of the National Academy of Sciences of the United States of America 93: 5925-5930 (1996)]. Early work on ER β focused on defining its affinity for a variety of ligands and indeed, some differences with ER α were seen. The tissue distribution of ER β has been well mapped in the rodent and it is not coincident with ER α . Tissues such as the mouse and rat uterus express predominantly ER α , whereas the mouse and rat lung express predominantly ER β [Couse, et al., Endocrinology 138: 4613-4621 (1997), Kuiper, et al., Endocrinology 138: 863-870 (1997)]. Even within the same organ, the distribution of ER α and ER β can be compartmentalized. For example, in the mouse ovary, ER β is highly expressed in the granulosa cells and ER α is restricted to the thecal and stromal cells [Sar and Welsch, Endocrinology 140: 963-971 (1999), Fitzpatrick, et al., Endocrinology 140: 2581-2591 (1999)]. However, there are examples where the receptors are coexpressed and there is evidence from in vitro studies that ER α and ER β can form heterodimers [Cowley, et al., Journal of Biological Chemistry 272: 19858-19862 (1997)].

A large number of compounds have been described that either mimic or block the activity of 17 β -estradiol. Compounds having roughly the same biological effects

as 17 β -estradiol, the most potent endogenous estrogen, are referred to as "estrogen receptor agonists". Those which, when given in combination with 17 β -estradiol, block its effects are called "estrogen receptor antagonists". In reality there is a continuum between estrogen receptor agonist and estrogen receptor antagonist activity and indeed some compounds behave as estrogen receptor agonists in some tissues and estrogen receptor antagonists in others. These compounds with mixed activity are called selective estrogen receptor modulators (SERMS) and are therapeutically useful agents (e.g. EVISTA) [McDonnell, Journal of the Society for Gynecologic Investigation 7: S10-S15 (2000), Goldstein, et al., Human Reproduction Update 6: 212-224 (2000)].

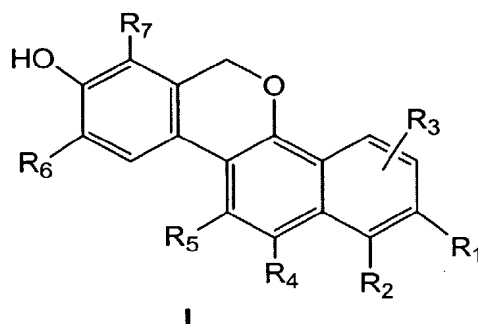
10 The precise reason why the same compound can have cell-specific effects has not been elucidated, but the differences in receptor conformation and/or in the milieu of coregulatory proteins have been suggested.

It has been known for some time that estrogen receptors adopt different conformations when binding ligands. However, the consequence and subtlety of these changes has been only recently revealed. The three dimensional structures of ER α and ER β have been solved by co-crystallization with various ligands and clearly show the repositioning of helix 12 in the presence of an estrogen receptor antagonist which sterically hinders the protein sequences required for receptor-coregulatory protein interaction [Pike, et al., Embo 18: 4608-4618 (1999), Shiau, et al., Cell 95: 927-937 (1998)]. In addition, the technique of phage display has been used to identify peptides that interact with estrogen receptors in the presence of different ligands [Paige, et al., Proceedings of the National Academy of Sciences of the United States of America 96: 3999-4004 (1999)]. For example, a peptide was identified that distinguished between ER α bound to the full estrogen receptor agonists 17 β -estradiol and diethylstilbesterol. A different peptide was shown to distinguish between clomiphene bound to ER α and ER β . These data indicate that each ligand potentially places the receptor in a unique and unpredictable conformation that is likely to have distinct biological activities.

As mentioned above, estrogens affect a panoply of biological processes. In addition, where gender differences have been described (e.g. disease frequencies, responses to challenge, etc), it is possible that the explanation involves the difference in estrogen levels between males and females.

DESCRIPTION OF THE INVENTION

This invention provides estrogenic compound of formula I having the structure,



wherein

- 5 R_1 and R_2 are each, independently, selected from hydrogen, hydroxyl, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, or halogen; wherein the the alkyl or alkenyl moieties of R_1 , or R_2 may be optionally substituted with hydroxyl, -CN, halogen, trifluoroalkyl, trifluoroalkoxy, -NO₂, or phenyl; and provided that at
- 10 least one of R_1 or R_2 is hydroxyl;
- R_3 , R_4 , R_5 , R_6 , and R_7 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, halogen, alkoxy of 1-6 carbon atoms, -CN, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, -CHO, phenyl, or a 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S; wherein the alkyl or
- 15 alkenyl moieties of R_4 , R_5 , R_6 , or R_7 may be optionally substituted with hydroxyl, -CN, halogen, trifluoroalkyl, trifluoroalkoxy, -NO₂, or phenyl; wherein the phenyl moiety of R_4 or R_5 may be optionally mono-, di-, or tri-substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, halogen, hydroxyl, alkoxy of 1-6 carbon atoms, -CN, -NO₂, amino, alkylamino of 1-6 carbon
- 20 atoms, dialkylamino of 1-6 carbon atoms per alkyl group, thio, alkylthio of 1-6 carbon atoms, alkylsulfinyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, alkoxycarbonyl of 2-7 carbon atoms, alkylcarbonyl of 2-7 carbon atoms, or benzoyl;
- or a pharmaceutically acceptable salt thereof.

25

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic,

malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable aids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, such as alkali metal salts (for example, sodium, lithium, or potassium) alkaline earth metal salts, ammonium salts, alkylammonium salts containing 1-6 carbon atoms or dialkylammonium salts containing 1-6 carbon atoms in each alkyl group, and trialkylammonium salts containing 1-6 carbon atoms in each alkyl group, when a compound of this invention contains an acidic moiety.

The terms alkyl and alkenyl as a group or part of a group, (e.g., alkoxy, alkylthio alkylcarbonyl), include both branched and straight chain moieties, e.g., of 1-6 and 2-7 carbon atoms respectively. Examples include methyl, ethyl, propyl, butyl, isopropyl, sec-butyl, tert-butyl, vinyl, allyl, 1-methyl vinyl, and the like. When alkyl or alkenyl moieties are substituted, they may typically be mono-, di-, tri- or persubstituted. Examples for a halogen substituent include 1-bromovinyl, 1-fluorovinyl, 1,2-difluorovinyl, 2,2-difluorovinyl, 1,2,2-trifluorovinyl, 1,2-dibromo ethane, 1,2-difluoroethane, 1-fluoro-2-bromo ethane, CF_2CF_3 , $\text{CF}_2\text{CF}_2\text{CF}_3$, and the like. The term halogen includes bromine, chlorine, fluorine, and iodine.

Preferred 5-6 membered heterocyclic rings include furan, thiophene, pyrrole, isopyrrole, pyrazole, imidazole, triazole, dithiole, oxathiole, isoxazole, oxazole, thiazole, isothiazole, oxadiazole, furazan, oxatriazole, dioxazole, oxathiazole, tetrazole, pyran, pyridine, pyridazine, pyrimidine, pyrazine, triazine, oxazine, oxathiazine, or oxadiazine. It is more preferred that the heterocyclic ring is furan or thiophene.

As used in accordance with this invention, the term "providing," with respect to providing a compound or substance covered by this invention, means either directly administering such a compound or substance, or administering a prodrug, derivative, or analog which will form the effective amount of the compound or substance within the body.

In some embodiments R_6 and R_7 are each, independently, hydrogen or halogen, for example R_6 is hydrogen or fluorine.

5 R_4 and R_5 may each for example be, independently, selected from hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, alkenyl of 2-7 carbon atoms, -CN, furyl and thienyl. In some embodiments R_4 is not hydrogen, e.g., R_4 is for example selected from cyano, chloro, bromo, methyl, ethyl, propyl, butyl, methoxy, vinyl, thien-2-yl and thien-3-yl.

10 Examples of R_5 are hydrogen and halogen, e.g., chlorine.

Examples of R_2 and R_3 are each, independently, hydrogen, halogen e.g., chlorine, or hydroxyl.

15 Examples of R_1 are hydrogen, hydroxyl and halogen, e.g., chlorine.

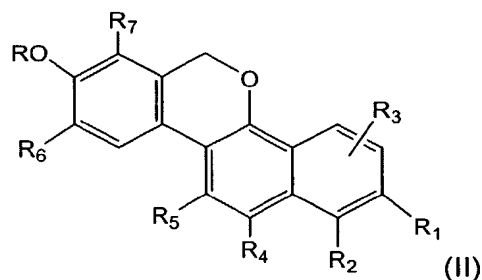
In some embodiments only one of R_1 and R_2 is hydroxy.

20 Examples of R_3 are hydrogen and halogen, such as chlorine, e.g., in the 4-position.

Of the compounds of this invention, it is preferred that R_6 and R_7 are each, independently, hydrogen or halogen; and R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, alkenyl of 25 2-7 carbon atoms, -CN, furyl, or thienyl. It is more preferred that R_1 , R_2 , and R_3 are each, independently, hydrogen, halogen, or hydroxyl; and still more preferred that R_4 is not hydrogen.

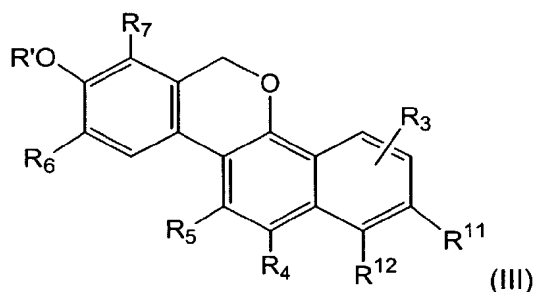
Also provided are processes for preparing the compounds of this invention. Accordingly this invention provides a process for preparing a compound of formula I which comprises one of the following:

a) de-alkylating a compound of formula II:



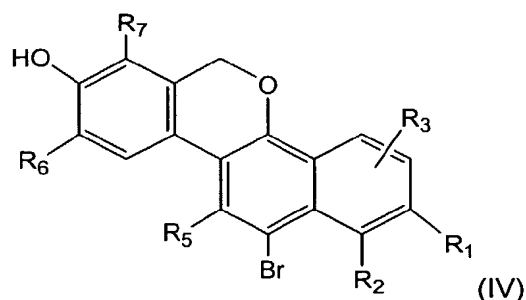
wherein R is an alkyl group of 1 to 6 carbon atoms and R₁, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined herein, to give a compound of formula I; or

- 5 b) de-acylating a compound of formula III:



- wherein R' is an acyl group, e.g., alkanoyl of 2-7 carbon atoms such as acetyl, R¹¹ is R₁ or an acyloxy group, e.g., alkanoyl of 2-7 carbon atoms such as acetyl, R¹² is R₂ or an acyloxy group, e.g., alkanoyl of 2-7 carbon atoms such as acetyl, and R₃, R₄, R₅,
 10 R₆, R₇, are as defined herein, to give a corresponding compound of formula I; or

- c) reacting a 12- bromo compound of formula IV:



- protected as necessary, wherein R₁, R₂, R₃, R₅, R₆ and R₇ are as defined herein, with
 15 an appropriate reactive derivative of formula:

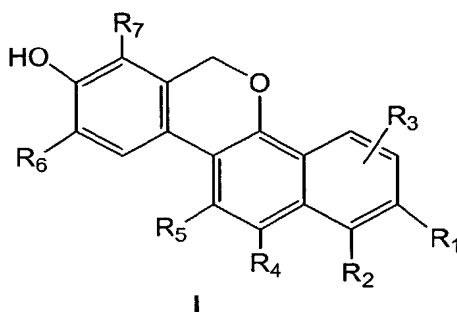


where R₄ is alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 7 carbon atoms or a 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S, and

where L is an appropriate leaving group, e.g., L is a boronic acid (such as butyl boronic acid or 2-thiophene boronic acid) or butyltin derivative (such as allyltributyltin); and removing any protecting groups, to give a corresponding compound of formula (I); or

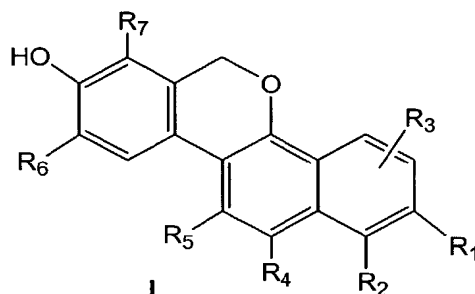
5

d) halogenating a compound of formula I:



as defined in claim 1 protected if necessary, and wherein at least one of R₁, R₂, R₃, R₄ and R₅ is hydrogen, with a halogenating agent, e.g., N-bromosuccinimide, N-chloro-succinimide followed if necessary by deprotection, to give a compound of formula I
10 wherein at least one of R₁, R₂, R₃ and R₄ is halogen; or

e) nitrilating (i.e., introducing CN) a compound of formula I:



15 as defined herein, protected as necessary, and wherein R₄ is bromine, with a nitrilating agent, e.g., zinc cyanide, followed if necessary by deprotection, to give a compound of formula I wherein R₄ is cyano; or

20 f) converting a basic compound of formula I to a pharmaceutically acceptable salt thereof or vice versa.

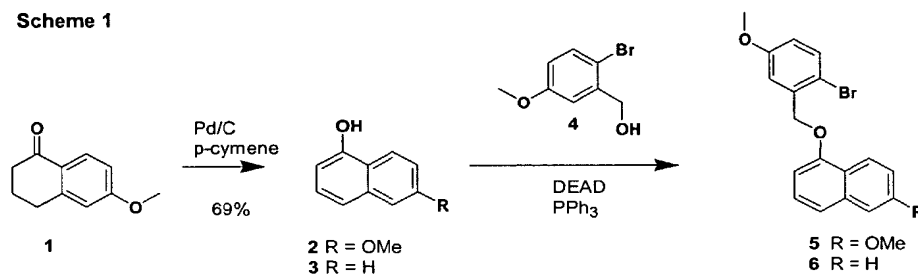
The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures

described in the literature. In any of the reactions described herein reactive substituent groups or sites may be protected prior to the reaction being carried out and the protecting group removed thereafter.

- 5 In process a) above where either of R_1 and R_2 is also alkoxy then this group may be dealkylated in the same reaction to give a corresponding compound of formula I wherein R_1 and/or R_2 is hydroxy.

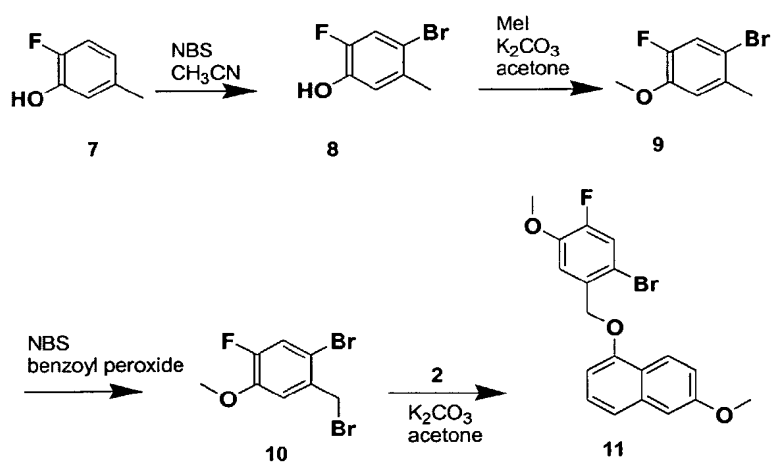
10 The preparation of several representative examples of this invention according to the processes above are described in the following Schemes 1-10.

Scheme 1

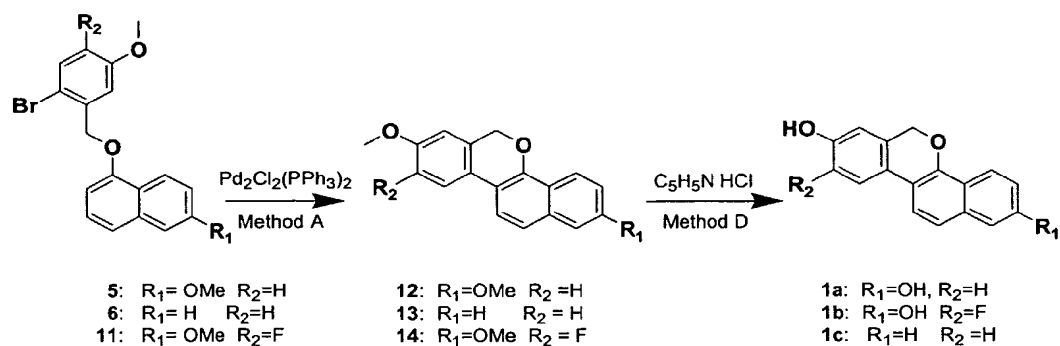


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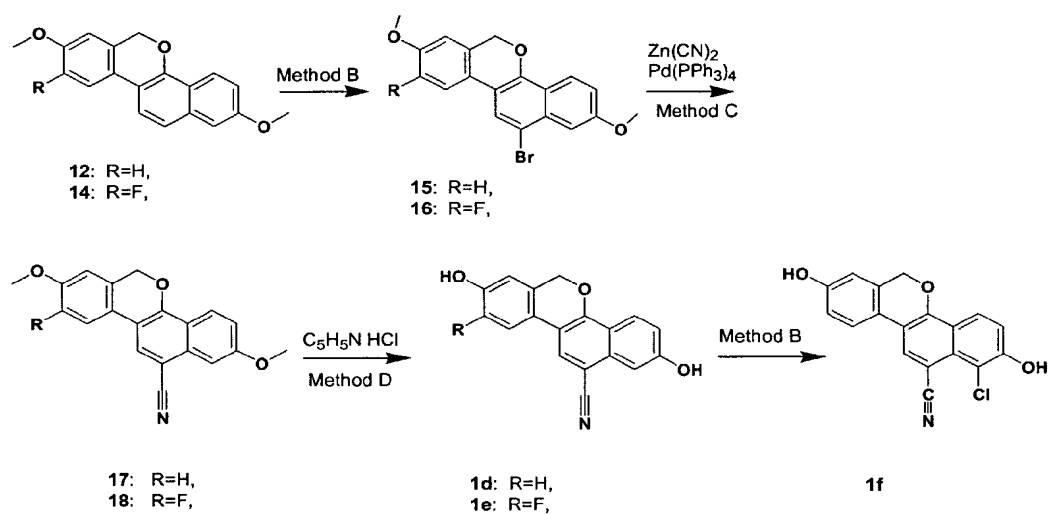
Scheme 2



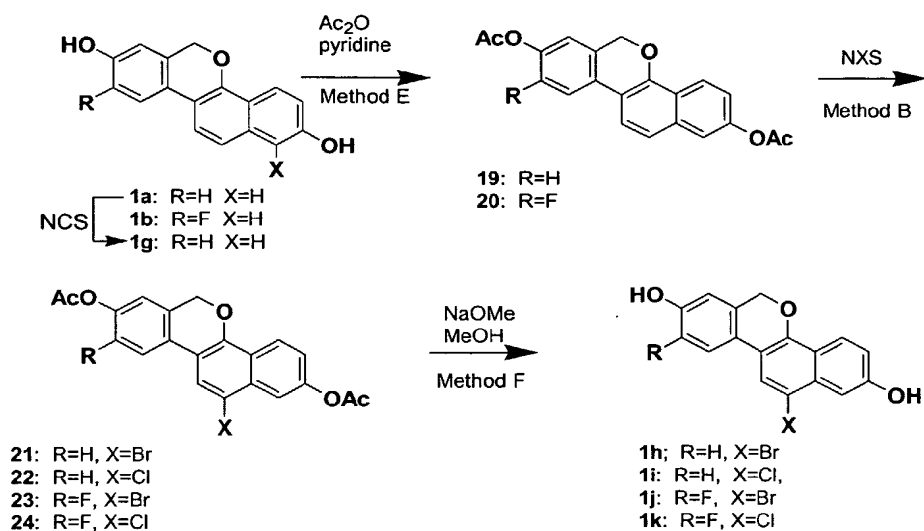
Scheme 3



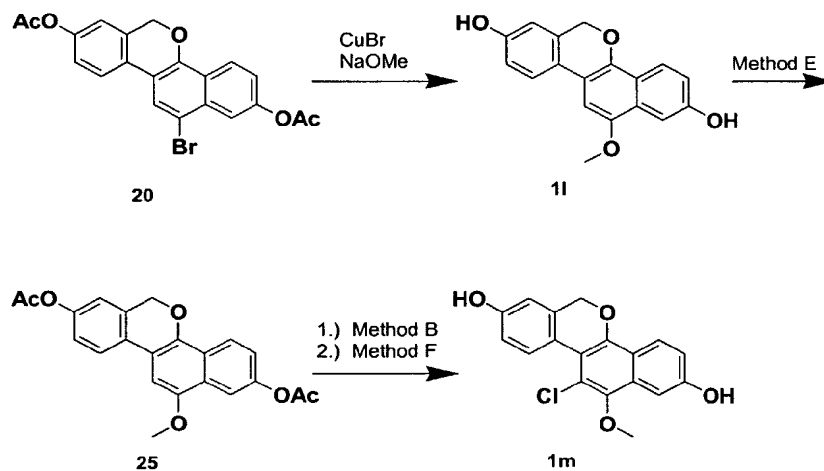
Scheme 4



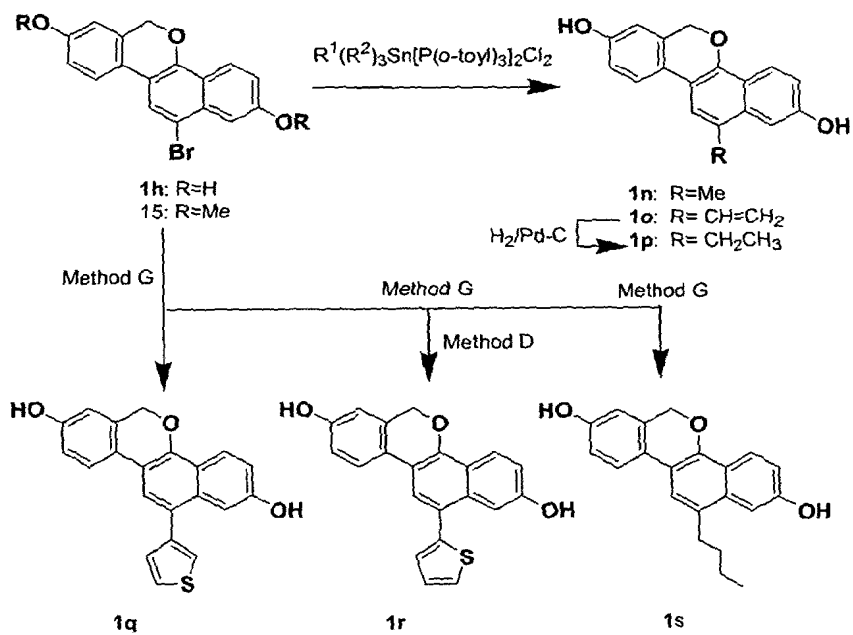
Scheme 5



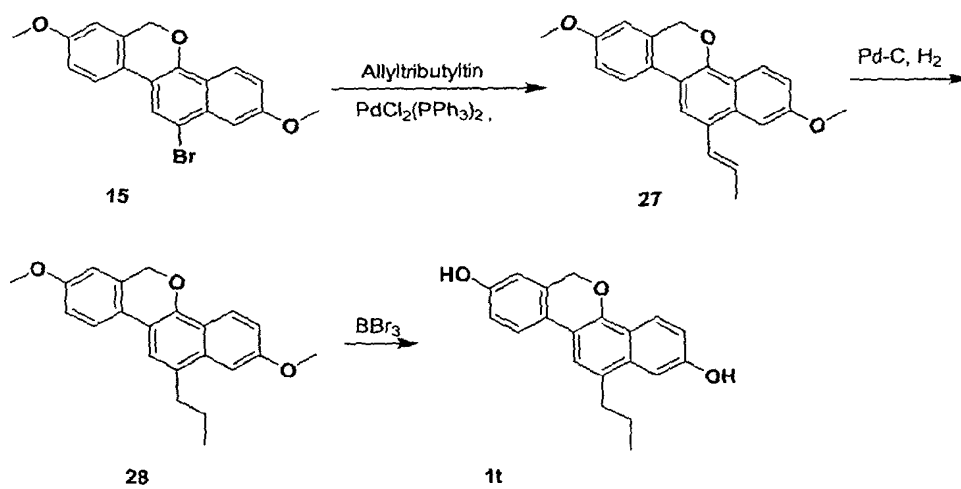
Scheme 6



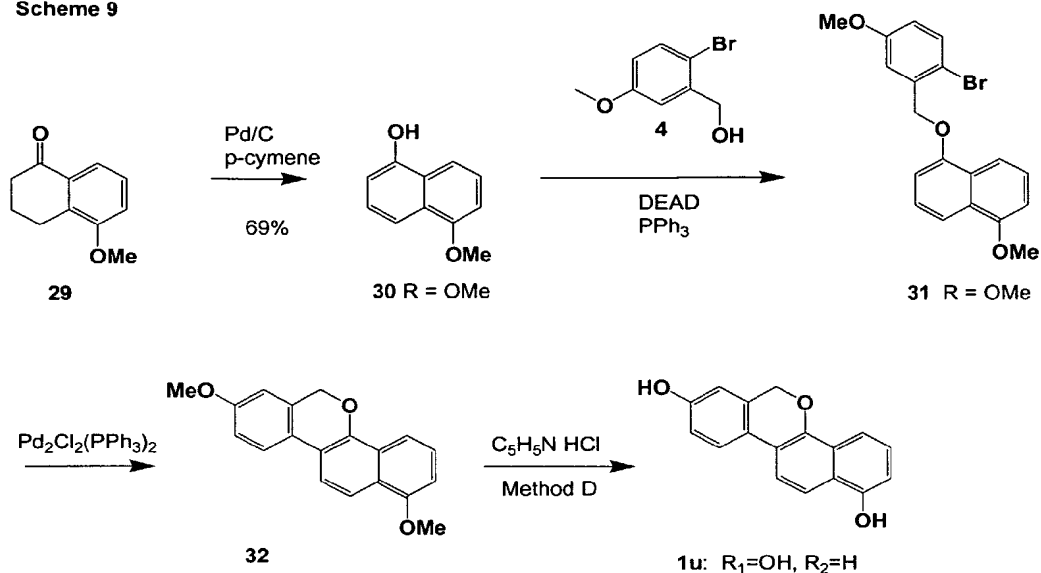
Scheme 7



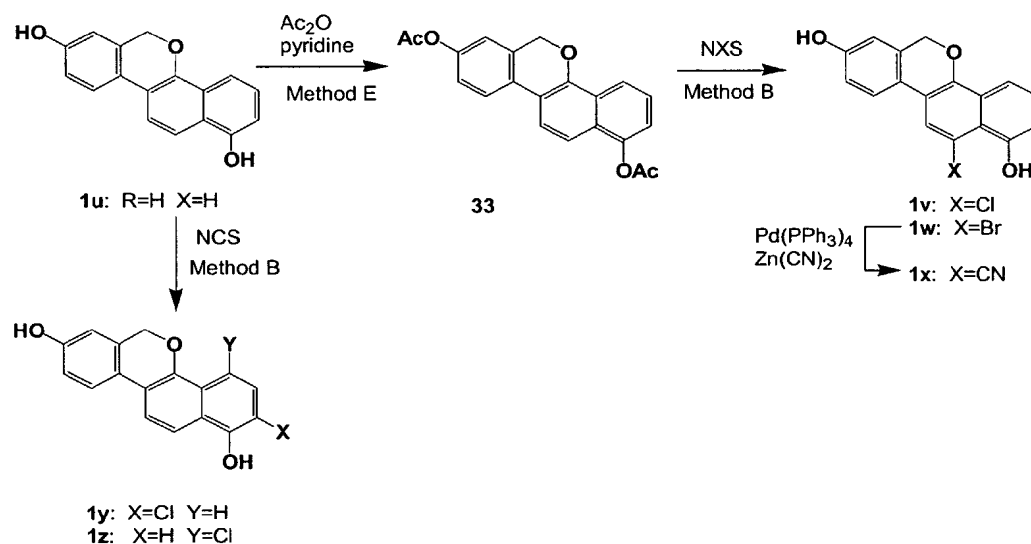
Scheme 8



Scheme 9



Scheme 10



5

Standard pharmacological test procedures are readily available to determine the activity profile of a given test compound. The following briefly summarizes several representative test procedures and may include data for representative compounds of the invention. All assays, except the radioligand binding assay, can be used to detect

estrogen receptor agonist or antagonist activity of compounds. In general, estrogen receptor agonist activity is measured by comparing the activity of the compound to a reference estrogen (e.g. 17β -estradiol, 17α -ethinyl, 17β -estradiol, estrone, diethylstilbesterol etc). Estrogen receptor antagonist activity is generally measured by co-

5 treating the test compound with the reference estrogen and comparing the result to that obtained with the reference estrogen alone. Standard pharmacological test procedures for SERMs are also provided in US Patents 4,418,068 and 5,998,402 which are hereby incorporated by reference.

10 Evaluation of binding affinities to ER α and ER β

Representative examples of the invention were evaluated for their ability to compete with 17β -estradiol for both ER α and ER β in a conventional radioligand binding assay. This test procedure provides the methodology for one to determine the relative binding affinities for the ER α or ER β receptors. The procedure used is

15 briefly described below.

Preparation of receptor extracts for characterization of binding selectivity. The ligand binding domains, conveniently defined here as all sequence downstream of the DNA binding domain, were obtained by PCR using full length cDNA as templates and primers that contained appropriate restriction sites for subcloning while maintaining

20 the appropriate reading frame for expression. These templates contained amino acids M₂₅₀-V₅₉₅ of human ER α [Green, et al., Nature 320: 134-9 (1986)] and M₂₁₄-Q₅₃₀ of human ER β [Ogawa, et al., Biochemical & Biophysical Research Communications 243: 122-6 (1998)]. Human ER β was cloned into pET15b (Novagen, Madison WI) as a Nco1-BamH1 fragment bearing a C-terminal Flag tag. Human ER α was cloned as

25 for human ER β except that an N-terminal His tag was added. The sequences of all constructs used were verified by complete sequencing of both strands.

BL21(DE3) cells were used to express the human proteins. Typically a 10 mL overnight culture was used to inoculate a 1 L culture of LB medium containing 100 μ g/mL of ampicillin. After incubation overnight at 37 °C, IPTG was added to a final

30 concentration of 1 mM and incubation proceeded at 25 °C for 2 hours. Cells were harvested by centrifugation (1500 x g), and the pellets washed with and resuspended in 100 mL of 50 mM Tris-Cl (pH 7.4), 150 mM NaCl. Cells were lysed by passing

twice through a French press at 12000 psi. The lysate was clarified by centrifugation at 12,000 x g for 30 minutes at 4°C and stored at -70°C.

Evaluation of extracts for specific [³H]-estradiol binding. Dulbecco's phosphate buffered saline (Gibco, 1x final concentration) supplemented with 1 mM EDTA was used as the assay buffer. To optimize the amount of receptor to use in the assay, [³H]-17β-estradiol (New England Nuclear; final concentration = 2 nM) ± 0.6 μM diethylstilbestrol and 100 μL of various dilutions of the E. coli lysate were added to each well of a high binding masked microtiter plate (EG&G Wallac). The final assay volume was 120 μL and the concentration of DMSO was ≤ 1%. After incubation at room temperature for 5-18 hours, unbound material was aspirated and the plate washed three times with approximately 300 μL of assay buffer. After washing, 135 μL of scintillation cocktail (Optiphase Supermix, EG&G Wallac) was added to the wells, and the plate was sealed and agitated for at least 5 minutes to mix scintillant with residual wash buffer. Bound radioactivity was evaluated by liquid scintillation counting (EG&G Wallac Microbeta Plus).

After determining the dilution of each receptor preparation that provided maximum specific binding, the assay was further optimized by estimating the IC₅₀ of unlabelled 17β-estradiol using various dilutions of the receptor preparation. A final working dilution for each receptor preparation was chosen for which the IC₅₀ of unlabelled 17β-estradiol was 2-4 nM.

Ligand binding competition test procedure. Test compounds were initially solubilized in DMSO and the final concentration of DMSO in the binding assay was ≤1%. Eight dilutions of each test compound were used as an unlabelled competitor for [³H]-17β-estradiol. Typically, a set of compound dilutions would be tested simultaneously on human ERα and ERβ. The results were plotted as measured DPM vs. concentration of test compound. For dose-response curve fitting, a four parameter logistic model on the transformed, weighted data was fit and the IC₅₀ was defined as the concentration of compound decreasing maximum [³H]-estradiol binding by 50%.

Binding affinities for ERα and ERβ (as measured by IC₅₀) for representative examples of the invention are shown in Table (1).

Table 1: ER binding affinities of representative compounds of the invention		
Example	ER- β IC ₅₀ (nM)	ER- α IC ₅₀ (nM)
1a	3.3	74
1b	1.8	20
1c	79.7	460
1d	1.8	107
1e	19	1231
1f	3.5	156
1g	2.7	74
1h	0.90	26
1i	1.1	17
1j	2.0	77
1k	2.0	27
1l	16	147
1m	0.27	10.4
1n	2.7	102
1o	2.3	81
1p	2.9	44
1q	29.2	154
1r	48.3	217
1s	3.0	71
1t	11	160
1u	1.4	17
1v	0.9	4.5
1w	1.4	10
1x	1.5	86
1y	1.65	17.6
1z	0.8	10

The results obtained in the standard pharmacologic test procedure described above demonstrate that the compounds of this invention bind both subtypes of the estrogen receptor. The IC₅₀s are generally lower for ER β , indicating these compounds are preferentially ER β selective ligands, but are still considered active at ER α . Compounds of this invention will exhibit a range of activity based, at least

partially, on their receptor affinity selectivity profiles. Since the compounds of the invention bind ER- β with higher affinity than ER- α , they will be useful in treating or inhibiting diseases that can be modulated via ER- β . Additionally, since each receptor ligand complex is unique and thus its interaction with various coregulatory proteins is unique, compounds of this invention will display different and unpredictable activities depending on cellular context. For example, in some cell-types, it is possible for a compound to behave as an estrogen receptor agonist while in other tissues, an estrogen receptor antagonist. Compounds with such activity have sometimes been referred to as SERMs (Selective Estrogen Receptor Modulators). Unlike many estrogens, however, many of the SERMs do not cause increases in uterine wet weight. These compounds are antiestrogenic in the uterus and can completely antagonize the trophic effects of estrogen receptor agonists in uterine tissue. These compounds, however, act as estrogen receptor agonists in the bone, cardiovascular, and central nervous systems. Due to this tissue selective nature of these compounds, they are useful in treating or inhibiting in a mammal disease states or syndromes which are caused or associated with an estrogen deficiency (in certain tissues such as bone or cardiovascular) or an excess of estrogen (in the uterus or mammary glands). In addition, compounds of this invention also have the potential to behave as estrogen receptor agonists on one receptor type while behaving as estrogen receptor antagonists on the other. For example, it has been demonstrated that compounds can be antagonize the action of 17 β -estradiol via ER β while exhibiting estrogen receptor agonist activity with ER α [Sun, et al., Endocrinology 140: 800-804 (1999)]. Such ERSAA (Estrogen Receptor Selective Agonist Antagonist) activity provides for pharmacologically distinct estrogenic activity within this series of compounds

Regulation of metallothionein II mRNA

Estrogens acting through ER β , but not ER α can upregulate metallothionein II mRNA levels in Saos-2 cells as described by Harris [Endocrinology 142: 645-652 (2001)]. Results from this test procedure can be combined with results from the test procedure described below (ERE reporter test procedure) to generate a selectivity profile for compounds of this invention (see also WO 00/37681).

Evaluation of test compound using an ERE-reporter test procedure in MCF-7 breast cancer cells

Stock solutions of test compounds (usually 0.1 M) are prepared in DMSO and then diluted 10 to 100-fold with DMSO to make working solutions of 1 or 10 mM. The

5 DMSO stocks are stored at either 4°C (0.1 M) or -20°C (< 0.1M). MCF-7 cells are passaged twice a week with growth medium [D-MEM/F-12 medium containing 10% (v/v) heat-inactivated fetal bovine serum, 1% (v/v) Penicillin-Streptomycin, and 2 mM glutaMax-1]. The cells are maintained in vented flasks at 37°C inside a 5% CO₂/95% humidified air incubator. One day prior to treatment, the cells are plated with growth

10 medium at 25,000 cells/well into 96 well plates and incubated at 37°C overnight.

The cells are infected for 2 hr at 37°C with 50 µl/well of a 1:10 dilution of adenovirus 5-ERE-tk-luciferase in experimental medium [phenol red-free D-MEM/F-12 medium containing 10% (v/v) heat-inactivated charcoal-stripped fetal bovine serum, 1% (v/v) Penicillin-Streptomycin, 2 mM glutaMax-1, 1 mM sodium pyruvate]. The wells

15 are then washed once with 150 µl of experimental medium. Finally, the cells are treated for 24 hr at 37 °C in replicates of 8 wells/treatment with 150 µl/well of vehicle (≤ 0.1% v/v DMSO) or compound that is diluted ≥ 1000-fold into experimental medium.

Initial screening of test compounds is done at a single dose of 1 µM that is

20 tested alone (estrogen receptor agonist mode) or in combination with 0.1 nM 17β-estradiol (EC₈₀; estrogen receptor antagonist mode). Each 96 well plate also includes a vehicle control group (0.1% v/v DMSO) and an estrogen receptor agonist control group (either 0.1 or 1 nM 17β-estradiol). Dose-response experiments are performed in either the estrogen receptor agonist and/or estrogen receptor antagonist

25 modes on active compounds in log increases from 10⁻¹⁴ to 10⁻⁵ M. From these dose-response curves, EC₅₀ and IC₅₀ values, respectively, are generated. The final well in each treatment group contains 5 µl of 3 x 10⁻⁵ M ICI-182,780 (10⁻⁶ M final concentration) as an estrogen receptor antagonist control.

After treatment, the cells are lysed on a shaker for 15 min with 25 µL/well of

30 1X cell culture lysis reagent (Promega Corporation). The cell lysates (20 µL) are transferred to a 96 well luminometer plate, and luciferase activity is measured in a MicroLumat LB 96 P luminometer (EG & G Berthold) using 100 µL/well of luciferase

substrate (Promega Corporation). Prior to the injection of substrate, a 1 second background measurement is made for each well. Following the injection of substrate, luciferase activity is measured for 10 seconds after a 1 second delay. The data are transferred from the luminometer to a Macintosh personal computer and analyzed using the JMP software (SAS Institute); this program subtracts the background reading from the luciferase measurement for each well and then determines the mean and standard deviation of each treatment.

The luciferase data are transformed by logarithms, and the Huber M-estimator is used to down-weight the outlying transformed observations. The JMP software is used to analyze the transformed and weighted data for one-way ANOVA (Dunnett's test). The compound treatments are compared to the vehicle control results in the estrogen receptor agonist mode, or the positive estrogen receptor agonist control results (0.1 nM 17 β -estradiol) in the estrogen receptor antagonist mode. For the initial single dose experiment, if the compound treatment results are significantly different from the appropriate control ($p < 0.05$), then the results are reported as the percent relative to the 17 β -estradiol control [i.e., ((compound - vehicle control)/(17 β -estradiol control - vehicle control)) x 100]. The JMP software is also used to determine the EC₅₀ and/or IC₅₀ values from the non-linear dose-response curves.

Evaluation of uterotrophic activity

Uterotrophic activity of a test compound can be measured according to the following standard pharmacological test procedures.

Procedure 1: Sexually immature (18 days of age) Sprague-Dawley rats are obtained from Taconic and provided unrestricted access to a casein-based diet (Purina Mills 5K96C) and water. On day 19, 20 and 21 the rats are dosed subcutaneously with 17 α -ethinyl-17 β -estradiol (0.06 μ g/rat/day), test compound or vehicle (50% DMSO/50% Dulbecco's PBS). To assess estrogen receptor antagonist, compounds are coadministered with 17 α -ethinyl-17 β -estradiol (0.06 μ g/rat/day). There are six rats/group and they are euthanized approximately 24 hours after the last injection by CO₂ asphyxiation and pneumothorax. Uteri are removed and weighed after trimming associated fat and expressing any internal fluid. A tissue sample can also be snap frozen for analysis of gene expression (e.g. complement factor 3 mRNA).

Procedure 2: Sexually immature (18 days of age) 129 SvE mice were obtained from Taconic and provided unrestricted access to a casein-based diet (Purina Mills 5K96C) and water. On day 22, 23, 24 and 25 the mice were dosed subcutaneously with compound or vehicle (corn oil). There were six mice/group and they were
 5 euthanized approximately 6 hours after the last injection by CO₂ asphyxiation and pneumothorax. Uteri were removed and weighed after trimming associated fat and expressing any internal fluid. The following results (Table (2)) were obtained for representative compounds from the invention.

Table 2: Evaluation of selected compounds in a mouse uterotrophic test procedure.	
Compound	mean uterine weight (mg) ± SEM
Vehicle	9.5 ± 0.3
17β-estradiol (50mg/kg)	46.7 ± 2.5
Example 1d (50mg/kg)	9.8 ± 0.5
Vehicle	10.3 ± 0.8
17β-estradiol (50mg/kg)	45.3 ± 1.9
Example 1i (50mg/kg)	28.9 ± 2.0

10

Evaluation of osteoporosis and lipid modulation (cardioprotection)

Female Sprague-Dawley rats, ovariectomized or sham operated, are obtained 1 day after surgery from Taconic Farms (weight range 240 - 275 g). They are housed 3 or 4 rats/cage in a room on a 12/12 (light/dark) schedule and provided with food
 15 (Purina 5K96C rat chow) and water ad libitum. Treatment for all studies begin 1 day after arrival and rats are dosed 7 days per week as indicated for 6 weeks. A group of age matched sham operated rats not receiving any treatment serve as an intact, estrogen replete control group for each study.

All test compounds are prepared in a vehicle of 50% DMSO (JT Baker, Phillipsburg, NJ) / 1x Dulbecco's phosphate saline (GibcoBRL, Grand Island, NY) at
 20 defined concentrations so that the treatment volume is 0.1 mL/100 g body weight. 17β-estradiol is dissolved in corn oil (20 µg/mL) and delivered subcutaneously, 0.1 mL/rat. All dosages are adjusted at three week intervals according to group mean body weight measurements, and given subcutaneously.

25 Five weeks after the initiation of treatment and one week prior to the termination of the study, each rat is evaluated for bone mineral density (BMD). The

total and trabecular density of the proximal tibia are evaluated in anesthetized rats using an XCT-960M (pQCT; Stratec Medizintechnik, Pforzheim, Germany). The measurements are performed as follows: Fifteen minutes prior to scanning, each rat is anesthetized with an intraperitoneal injection of 45 mg/kg ketamine, 8.5 mg/kg xylazine, and 1.5 mg/kg acepromazine.

5 The right hind limb is passed through a polycarbonate tube with a diameter of 25 mm and taped to an acrylic frame with the ankle joint at a 90° angle and the knee joint at 180°. The polycarbonate tube is affixed to a sliding platform that maintains it perpendicular to the aperture of the pQCT. The platform is adjusted so that the distal
10 end of the femur and the proximal end of the tibia is in the scanning field. A two dimensional scout view is run for a length of 10 mm and a line resolution of 0.2 mm. After the scout view is displayed on the monitor, the proximal end of the tibia is located. The pQCT scan is initiated 3.4 mm distal from this point. The pQCT scan is 1 mm thick, has a voxel (three dimensional pixel) size of 0.140 mm, and consists of
15 145 projections through the slice.

After the pQCT scan is completed, the image is displayed on the monitor. A region of interest including the tibia but excluding the fibula is outlined. The soft tissue is mathematically removed using an iterative algorithm. The density of the remaining bone (total density) is reported in mg/cm^3 . The outer 55% of the bone is
20 mathematically peeled away in a concentric spiral. The density of the remaining bone (Trabecular density) is reported in mg/cm^3 .

One week after BMD evaluation the rats are euthanized by CO_2 asphyxiation and pneumothorax, and blood is collected for cholesterol determination. The uteri are also removed and the weighed after trimming associated fat and expressing any
25 luminal fluid. Total cholesterol is determined using a Boehringer-Mannheim Hitachi 911 clinical analyzer using the Cholesterol/HP kit. Statistics were compared using one-way analysis of variance with Dunnet's test.

Evaluation of antioxidant activity

30 Porcine aortas are obtained from an abattoir, washed, transported in chilled PBS, and aortic endothelial cells are harvested. To harvest the cells, the intercostal vessels of the aorta are tied off and one end of the aorta clamped. Fresh, sterile filtered, 0.2% collagenase (Sigma Type I) is placed in the vessel and the other end of the vessel then clamped to form a closed system. The aorta is incubated at 37 °C for

15-20 minutes, after which the collagenase solution is collected and centrifuged for 5 minutes at 2000 x g. Each pellet is suspended in 7 mL of endothelial cell culture medium consisting of phenol red free DMEM/Ham's F12 media supplemented with charcoal stripped FBS (5%), NuSerum (5%), L-glutamine (4 mM), penicillin-streptomycin (1000 U/ml, 100 µg/ml) and gentamycin (75 µg/ml), seeded in 100 mm petri dish and incubated at 37°C in 5%CO₂. After 20 minutes, the cells are rinsed with PBS and fresh medium added, this was repeated again at 24 hours. The cells are confluent after approximately 1 week. The endothelial cells are routinely fed twice a week and, when confluent, trypsinized and seeded at a 1:7 ratio. Cell mediated oxidation of 12.5 µg/mL LDL is allowed to proceed in the presence of the compound to be evaluated (5 µM) for 4 hours at 37°C. Results are expressed as the percent inhibition of the oxidative process as measured by the TBARS (thiobarbituric acid reactive substances) method for analysis of free aldehydes [Yagi, Biochemical Medicine 15: 212-6 (1976)].

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Progesterone receptor mRNA regulation standard pharmacological test procedure

This test procedure can be used to evaluate the estrogenic or antiestrogenic activity of compounds from this invention [Shughrue, et al., Endocrinology 138: 5476-5484 (1997)]. Data for representative compounds of the invention are shown in Table (3).

20

Table 3. Effect of representative compounds of the invention on regulation of progesterone mRNA in the preoptic area of the rat brain	
Compound (10mg/kg)	Progesterone receptor mRNA (arbitrary units; mean ± stdev)
Vehicle	189.2 ± 27.2
Example 1d	403.9 ± 19.1
Vehicle	4.3 ± 1.5
Example 1i	57.5 ± 14.0

Rat Hot Flush Test Procedure

The effect of test compounds on hot flushes can be evaluated in a standard pharmacological test procedure which measures the ability of a test compound to blunt the increase in tail skin temperature which occurs as morphine-addicted rats are acutely withdrawn from the drug using naloxone [Merchenthaler, et al., Maturitas 30:

307-16 (1998)]. It can also be used to detect estrogen receptor antagonist activity by co-dosing test compound with the reference estrogen.

Evaluation of vasomotor function in isolated rat aortic rings

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Sprague-Dawley rats (240-260 grams) are divided into 4 groups:

1. Normal non-ovariectomized (intact)
2. Ovariectomized (ovex) vehicle treated
3. Ovariectomized 17 β -estradiol treated (1 mg/kg/day)
- 10 4. Ovariectomized animals treated with test compound (various doses)

Animals are ovariectomized approximately 3 weeks prior to treatment. Each animal receives either 17- β estradiol sulfate (1 mg/kg/day) or test compound suspended in distilled, deionized water with 1% tween-80 by gastric gavage. Vehicle
15 treated animals received an appropriate volume of the vehicle used in the drug treated groups.

Animals are euthanized by CO₂ inhalation and exsanguination. Thoracic aortae are rapidly removed and placed in 37°C physiological solution with the following composition (mM): NaCl (54.7), KCl (5.0), NaHCO₃ (25.0), MgCl₂ 2H₂O
20 (2.5), D-glucose (11.8) and CaCl₂ (0.2) gassed with CO₂-O₂, 95%/5% for a final pH of 7.4. The adventitia is removed from the outer surface and the vessel is cut into 2-3 mm wide rings. Rings are suspended in a 10 mL tissue bath with one end attached to the bottom of the bath and the other to a force transducer. A resting tension of 1 gram is placed on the rings. Rings are equilibrated for 1 hour, signals are acquired
25 and analyzed.

After equilibration, the rings are exposed to increasing concentrations of phenylephrine (10⁻⁸ to 10⁻⁴ M) and the tension recorded. Baths are then rinsed 3 times with fresh buffer. After washout, 200 mM L-NAME is added to the tissue bath and equilibrated for 30 minutes. The phenylephrine concentration response curve is then
30 repeated.

Evaluation of cardioprotective activity

Apolipoprotein E-deficient C57/B1J (apo E KO) mice are obtained from Taconic Farms. All animal procedures are performed under strict compliance to
35 IACUC guidelines. Ovariectomized female apo E KO mice, 4-7 weeks of age, are housed in shoe-box cages and were allowed free access to food and water. The

animals are randomized by weight into groups (n=12-15 mice per group). The animals are dosed with test compounds or estrogen (17 β -estradiol sulfate at 1 mg/kg/day) in the diet using a Precise-dosing Protocol, where the amount of diet consumed is measured weekly, and the dose adjusted accordingly, based on animal weight. The diet used is a Western-style diet (57U5) that is prepared by Purina and contains 0.50% cholesterol, 20% lard and 25 IU/KG Vitamin E. The animals are dosed/fed using this paradigm for a period of 12 weeks. Control animals are fed the Western-style diet and receive no compound. At the end of the study period, the animals are euthanized and plasma samples obtained. The hearts are perfused in situ, first with saline and then with neutral buffered 10% formalin solution.

For the determination of plasma lipids and lipoproteins, total cholesterol and triglycerides are determined using enzymatic methods with commercially available kits from Boehringer Mannheim and Wako Biochemicals, respectively and analyzed using the Boehringer Mannheim Hitachi 911 Analyzer. Separation and quantification of plasma lipoproteins were performed using FPLC size fractionation. Briefly, 50-100 mL of serum is filtered and injected into Superose 12 and Superose 6 columns connected in series and eluted at a constant flow rate with 1 mM sodium EDTA and 0.15 M NaCl. Areas of each curve representing VLDL, LDL and HDL are integrated using Waters Millennium™ software, and each lipoprotein fraction is quantified by multiplying the Total Cholesterol value by the relative percent area of each respective chromatogram peak.

For the quantification of aortic atherosclerosis, the aortas are carefully isolated and placed in formalin fixative for 48-72 hours before handling. Atherosclerotic lesions are identified using Oil Red O staining. The vessels are briefly destained, and then imaged using a Nikon SMU800 microscope fitted with a Sony 3CCD video camera system in concert with IMAQ Configuration Utility (National Instrument) as the image capturing software. The lesions are quantified en face along the aortic arch using a custom threshold utility software package (Coleman Technologies). Automated lesion assessment is performed on the vessels using the threshold function of the program, specifically on the region contained within the aortic arch from the proximal edge of the brachio-cephalic trunk to the distal edge of the left subclavian artery. Aortic atherosclerosis data are expressed as percent lesion involvement strictly within this defined luminal area.

Evaluation of cognition enhancement

Ovariectomized rats (n=50) are habituated to an 8-arm radial arm maze for 10-min periods on each of 5 consecutive days. Animals are water-deprived prior to habituation and testing. A 100 µL aliquot of water placed at the ends of each arm serves as reinforcement. Acquisition of a win-shift task in the radial arm maze is accomplished by allowing the animal to have access to one baited arm. After drinking, the animal exits the arm and re-enters the central compartment, where it now has access to the previously visited arm or to a novel arm. A correct response is recorded when the animal chooses to enter a novel arm. Each animal is given 5 trials per day for 3 days. After the last acquisition trial, the animals are assigned to one of the following 4 groups:

1. Negative controls: injected with 10% DMSO/ sesame oil vehicle once daily for 6 days (1 mL/kg, SC)
2. Positive controls: injected with 17β-estradiol benzoate for 2 days and tested 4 days after the second injection (17β-estradiol benzoate at 10 µg/0.1 mL per rat)
3. Estradiol: 17β-estradiol will be injected daily for 6 days (20 µg/kg, SC)
4. Test compound: injected daily for 6 days (doses vary).

All injections will begin after testing on the last day of acquisition. The last injection for groups 1, 3, and 4 will take place 2 hours before testing for working memory.

The test for working memory is a delayed non-matching-to-sample task (DNMS) utilizing delays of 15, 30, or 60 seconds. This task is a variation of the acquisition task in which the rat is placed in the central arena and allowed to enter one arm as before. A second arm is opened once the rat traverses halfway down the first arm, and again the rat is required to choose this arm. When it has traveled halfway down this second arm, both doors are closed and the delay is instituted. Once the delay has expired, both of the original two doors, and a third novel door, are opened simultaneously. A correct response is recorded when the animal travels halfway down the third, novel arm. An incorrect response is recorded when the animal travels halfway down either the first or second arms. Each animal will receive 5 trials at each of the three delay intervals for a total of 15 trials per subject.

Evaluation of effect on pleurisy

The ability to reduce the symptoms of experimentally-induced pleurisy in rats can be evaluated according to the procedure of Cuzzocrea [Endocrinology 141: 1455-63 (2000)].

5

Evaluation of protection against glutamate-induced cytotoxicity (neuroprotection)

The neuroprotective activity of compounds of this invention can be evaluated in an in vitro standard pharmacological test procedure using glutamate challenge [Zaulyanov, et al., Cellular & Molecular Neurobiology 19: 705-18 (1999); Prokai, et al., Journal of Medicinal Chemistry 44: 110-4 (2001)].

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Evaluation in the Mammary End Bud Test Procedure

Estrogens are required for full ductal elongation and branching of the mammary ducts, and the subsequent development of lobulo-alveolar end buds under the influence of progesterone. In this test procedure, the mammotrophic activity of selected compounds of the invention was evaluated according to the following standard pharmacological test procedure. Twenty-eight day old Sprague-Dawley rats (Taconic Farms, Germantown, NY) were ovariectomized and rested for nine days. Animals were housed under a 12-hour light/dark cycle and fed a casein-based Purina Laboratory Rodent Diet 5K96 (Purina, Richmond, IN) and allowed free access to water. Rats were then dosed subcutaneously for six days with vehicle (50% DMSO (JT Baker, Phillipsburg, NJ) / 50% 1x Dulbecco's Phosphate buffered saline (GibcoBRL, Grand Island, NY), 17 β -estradiol (0.1 mg/kg) or test compound (20 mg/kg). For the final three days, rats were also dosed subcutaneously with progesterone (30 mg/kg). On the seventh day, rats were euthanised and a mammary fat pad excised. This fat pad was analyzed for casein kinase II mRNA as a marker of end bud proliferation. Casein kinase II mRNA was analyzed by real-time RT-PCR. Briefly, RNA was isolated following Trizol (GibcoBRL, Grand Island, NY) according to the manufacture's directions. Samples were treated with DNase I using DNA-free kit (Ambion), and casein kinase II mRNA levels were measured by real-time RT-PCR using the Taqman Gold procedure (PE Applied Biosystems). A total of 50 ng of RNA was analyzed in triplicate using casein kinase II specific primer pair (5' primer, CACACGGATGGCGCATACT; 3' primer, CTCGGGATGCACCATGAAG) and customized probe (TAMRA-CGGCACTGGTTTCCCTCACATGCT-FAM). Casein

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kinase II mRNA levels were normalized to 18s ribosomal RNA contained within each sample reaction using primers and probe supplied by PE Applied Biosystems. The following results were obtained for an example of the invention (Table (4)).

Table 4: Evaluation of compounds in a rat mammotrophic assay	
Compound	Casein kinase II mRNA/18S rRNA (mean \pm SEM)
Vehicle + progesterone (30mg/kg)	1.61 \pm 0.36
17 β -estradiol (0.1 mg/kg) + progesterone (30 mg/kg)	39.0 \pm 5.4
Example 1d (20 mg/kg) + progesterone (30 mg/kg)	1.4 \pm 0.7

5

Evaluation in the HLA Rat Standard Pharmacological Test Procedure for inflammatory bowel disease

Representative compounds of the invention were evaluated in the HLA rat standard pharmacological test procedure which emulates inflammatory bowel disease in humans. The following briefly describes the procedure used and results obtained. Male HLA-B27 rats were obtained from Taconic and provided unrestricted access to food (PMI Lab diet 5001) and water. Rats were dosed once daily (orally) with either vehicle (2% tween-80/0.5% methylcellulose) or Example 1d (10 mg/kg) for 26 days. Stool quality was observed daily and graded according to the following scale: Diarrhea = 3; soft stool = 2; normal stool = 1. Table (5) shows that stool quality improved after dosing with Example 1d. At the end of the study, serum was collected and stored at -70°C . A section of colon was prepared for histological analysis and an additional segment was analyzed for myeloperoxidase activity.

20

Table 5: Evaluation of stool character of HLA rats treated orally with vehicle or a representative compound from the invention. Value reported is the group's average score.		
Day	Vehicle	Example 1d
1	1	1
2	1	1
3	1	1
4	1.25	1
5	2.5	1.5
6	2.75	1.25
7	2.75	1.25
8	2.75	1
9	3	1.25
10	3	1
11	2.75	1.25
12	2.75	1.25
13	2.75	1.25
14	2.75	1.25
15	2.75	1
16	3	1
17	2.75	1
18	2.75	1
19	2.75	1
20	ND	ND
21	ND	ND
22	3	1
23	3	1
24	3	1
25	3	1
26	3	1
ND: Not determined 3= diarrhea; 2= soft stool; 1=normal stool		

- Histological analysis. Colonic tissue was immersed in 10% neutral buffered formalin. Each specimen of colon was separated into four samples for evaluation.
- 5 The formalin-fixed tissues were processed in a Tissue Tek vacuum infiltration processor (Miles, Inc; West Haven, Connecticut) for paraffin embedding. The samples were sectioned at 5 μ m and then stained with hematoxylin and eosin (H&E) for blinded histologic evaluations using a scale modified after Boughton-Smith. After the scores were completed the samples were unblinded, and data were tabulated and
- 10 analyzed by ANOVA linear modeling with multiple mean comparisons. Sections of colonic tissue were evaluated for several disease indicators and given relative scores. As shown in Table (6), Example 1d is effective in reducing several measurements of tissue injury.

Table 6: Histological scoring of disease severity in the colon from animals treated orally for 4 weeks with a representative compound from the invention . Means \pm SD

Group	Ulceration (0-2)	Inflammation (0-3)	Lesion depth (0-2)	Fibrosis (0-2)	Total score
Vehicle	1.44 \pm 0.66	2.88 \pm 0.14	1.56 \pm 0.63	1.06 \pm 0.32	6.94 \pm 1.51
Example 1d	0.19 \pm 0.13*	1.38 \pm 0.43*	0.19 \pm 0.13*	0.13 \pm 0.14*	1.88 \pm 0.14*
* sig < vehicle					

Evaluation in two models of arthritis

Lewis rat assay of adjuvant-induced arthritis. Sixty, female, 12 weeks old, Lewis rats are housed according to standard facility operating procedures. They receive a standard regimen of food and water ad libitum. Each animal is identified by a cage card indicating the project group and animal number. Each rat number is marked by indelible ink marker on the tail. At least 10-21 days before study they are anesthetized and ovariectomized by standard aseptic surgical techniques.

Freund's Adjuvant-Complete (Sigma Immuno Chemicals, St. Louis, MO) is used to induce arthritis, each mL containing 1 mg Mycobacterium tuberculosis heat killed and dried, 0.85 mL mineral oil and 0.15 mL mannide monooleate Lot No. 084H8800.

The following are examples of two test procedures. Inhibition test procedure: Thirty rats are injected intradermally with 0.1 mL of Freund's Adjuvant-Complete at the base of the tail. The animals are randomized to four groups, each group containing six rats. Each day, the groups receive vehicle (50% DMSO (JT Baker, Phillipsburg, NJ) / 1x Dulbecco's phosphate saline (GibcoBRL, Grand Island, NY)) or test compound (10 mg/kg, administered subcutaneously). All rats begin treatment on Day 1. Data for a representative compound of the invention is shown in Table (7).

Treatment test procedure: Thirty rats are injected intradermally with 0.1 mL of Freund's Adjuvant-Complete at the base of the tail. The animals are randomized to four groups, each group containing six rats. Each day, the groups receive vehicle (50% DMSO (JT Baker, Phillipsburg, NJ) / 1x Dulbecco's phosphate saline (GibcoBRL, Grand Island, NY)) or test compound (10 mg/kg administered subcutaneously). All rats begin treatment on Day 8 after adjuvant injection. Data for a representative compound of the invention are shown in Tables (8), (9) and (10).

Statistical analysis was performed using Abacus Concepts Super ANOVA. (Abacus Concepts, Inc., Berkeley, CA). All of the parameters of interest were subjected to Analysis of Variance with Duncan's new multiple range post hoc testing

between groups. Data are expressed throughout as mean \pm standard deviation (SD), and differences were deemed significant if $p < 0.05$.

The degree of arthritis severity is monitored daily in terms of the following disease indices: Hindpaw erythema, hindpaw swelling, tenderness of the joints, and movements and posture. An integer scale of 0 to 3 is used to quantify the level of erythema (0= normal paw, 1= mild erythema, 2= moderate erythema, 3= severe erythema) and swelling (0=normal paw, 1=mild swelling, 2= moderate swelling, 3= severe swelling of the hind paw). The maximal score per day is 12.

At the end of the study the rats are euthanized with CO₂, hindlimbs removed at necropsy and fixed in 10% buffered formalin, and the tarsal joints decalcified and embedded in paraffin. Histologic sections are stained with Hematoxylin and Eosin or Saffranin O - Fast Green stain.

Slides are coded so that the examiner is blinded to the treatment groups. Synovial tissue from tarsal joints is evaluated based on synovial hyperplasia, inflammatory cell infiltration, and pannus formation [Poole and Coombs, International Archives of Allergy & Applied Immunology 54: 97-113 (1977)] as outlined below.

Category	Grade
1. Synovial lining cells	
a. No change	0
b. Cells enlarged, slightly thickened	1
c. Cells enlarged, increase in numbers, moderately thickened. No villus present	2
d. Cells enlarged, thickened. Villus present	3
2. Fibroplasia	
a. No change	0
b. Fibroplasia present under lining cells	1
c. Small areas of areolar tissue replaced by fibrous tissue	2
d. Replacement of areolar tissue by fibrous tissue	3
3. Inflammatory cells	
a. Occasionally seen, scattered throughout selection	0
b. Cells present in small numbers in or just under lining cell layer and/or around blood vessels.	1
c. Small focal collection of cells may be present	2
d. Large numbers of cells present in capsule and in or under lining cell layers. Large foci often seen.	3
4. Pannus	
a. Not detectable	0
b. Detectable	1

In addition, articular cartilage and bone is evaluated using Mankin's histological grading system [Mankin, et al., Journal of Bone & Joint Surgery - American Volume 53: 523-37 (1971)] as shown below.

Category	Grade
1. Structure	
a. Normal	0
b. Surface irregularity	1
c. Pannus and surface irregularity	2
d. Clefts to transitional zone	3
e. Clefts to radial zone	4
f. Clefts to calcified zone	5
g. Complete disorganization	6
2. Cells	
a. Normal	0
b. Diffuse hypercellularity	1
c. Cloning	2
d. Hypocellularity	3
3. Safranin-O staining	
a. Normal	0
b. Slight reduction	1
c. Modest reduction	2
d. Severe reduction	3
e. No dye noted	4
4. Tidemark integrity	
a. Intact	0
b. Crossed by blood vessels	1

5

Table 7: Evaluation of joint inflammation of Lewis rats: Inhibition protocol		
Day	Vehicle	Example 1d
1	0.00	0.00
2	0.00	0.00
3	4.50	2.66
4	5.50	1.83
5	9.33	2.66
6	10.50	2.16
7	10.60	2.00
8	11.00	1.66
9	11.50	2.00
10	11.33	2.00
11	10.83	1.66
12	10.83	1.66
13	11.00	2.16
14	11.00	2.00
15	11.00	2.00
16	11.00	1.00
17	10.50	1.33

Table 8: Evaluation of joint inflammation of Lewis rats: Treatment protocol		
Day	Vehicle	Example 1d
1	10.83	11.33
2	11.00	11.15
3	10.83	11.33
4	11.33	9.83
5	11.50	8.83
6	11.50	7.83
7	11.50	6.16
8	11.50	5.00
9	11.00	4.33
10	11.00	2.66
11	10.66	1.83
12	10.66	1.83
13	10.50	2.66
14	9.83	2.66
15	8.10	2.00
16	7.35	2.00
17	6.50	1.50

Table 9: Histological scoring of synovitis in the tarsal joints of Lewis rats (mean \pm SD): Treatment protocol					
Group	Synovial Structure (0-3)	Fibroplasia (0-3)	Inflammatory Cells (0-3)	Pannus (0-1)	Total Synovitis Score (0-10)
Vehicle	2.58 \pm 0.38	1.75 \pm 0.42	2.92 \pm 0.20	1.00 \pm 0.89	8.25 \pm 1.57
Example 1d (10mg/kg)	1.75 \pm 0.52*	0.75 \pm 0.42*	1.33 \pm 0.41*	0.08 \pm 0.20*	3.92 \pm 1.36*
* sig < vehicle					

5

Table 10: Histological scoring of cartilage change (Mankin scores) in the tarsal joints of Lewis rats (mean \pm SD): Treatment protocol					
Group	Cartilage Structure (0-6)	Cartilage Cells (0-3)	Safranin-O/ Fast Green Staining (0-4)	Tidemark Integrity (0-1)	Total Mankin Score (0-14)
Vehicle	2.83 \pm 0.26	2.58 \pm 0.38	2.50 \pm 0.32	0	7.92 \pm 0.74
Example 1d (10mg/kg)	1.67 \pm 0.41*	0.58 \pm 0.38*	1.25 \pm 0.61*	0	3.50 \pm 1.27*
* sig < vehicle					

Evaluation in the HLA-B27 Rat model of arthritis. Representative compounds of the invention were evaluated in the HLA-B27 rat standard pharmacological test procedure which emulates arthritis in humans. The following briefly describes the procedure used and results obtained. Male HLA-B27 rats (8-10 weeks old) were obtained from Taconic and provided unrestricted access to a food (PMI Lab diet 5001) and water. Rats were dosed orally once daily with either vehicle (2% tween-80/0.5% methylcellulose) or test compound (10 mg/kg) for 26 days. Joint scores and histology are evaluated as described above for the Lewis rat model of adjuvant-induced arthritis. Data for a representative compound of the invention is shown in Table (11).

Table 11: Evaluation of joint inflammation of HLA rats from Study 2.

Day	Vehicle	Example 1d
1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
6	0	0
7	0	0
8	2.5	2
9	3.75	1.25
10	2.75	1
11	3.5	0
12	1.25	0.5
13	1.25	0.25
14	1.25	0
15	5.25	0.25
16	4.5	1
17	3.5	1
18	3.75	0.5
19	5.5	0.75
22	3.25	0.25
23	6.5	2
24	6.5	2
25	6.25	2
26	7	1.75

Evaluation in in vivo models of carcinogenesis

The ability of compounds of this invention to treat and inhibit various malignancies or hyperproliferic disorders can be evaluated in standard pharmacological

test procedures that are readily available in the literature, and include the following two procedures.

Breast cancer. Athymic nu/nu (nude) mice are obtained ovariectomized from Charles River Laboratories (Wilmington, MA). One day prior to tumor cell injection, animals are implanted with time-release pellets containing 0.36-1.7 mg 17 β -estradiol (60 or 90 day release, Innovative Research of America, Sarasota, FL) or a placebo. The pellet is introduced subcutaneously into the intrascapular region using a 10-gauge precision trochar. Subsequently, mice are injected subcutaneously into the breast tissue with either 1x10⁷ MCF-7 cells or 1x10⁷ BG-1 cells. The cells are mixed with an equal volume of matrigel, a basement membrane matrix preparation to enhance tumor establishment. Test compounds can be evaluated either by dosing one day after tumor cell implantation (inhibition regimen) or after tumors have reached a certain size (treatment regimen). Compounds are administered either intraperitoneally or orally in a vehicle of 1% tween-80 in saline each day. Tumor size is evaluated every three or seven days.

Colon cancer. The ability to treat or inhibit colon cancer can be evaluated in the test procedure of Smirnoff [Oncology Research 11: 255-64 (1999)].

Evaluation of neuroprotection in two in vivo test procedures

Transient global ischemia in the Mongolian gerbil. The effect of test compounds on preventing or treating brain injury in response to oxygen deprivation/reperfusion can be measured using the following test procedure.

Female Mongolian gerbils (60-80 g; Charles River Laboratories, Kingston, NY) are housed in the Wyeth-Ayerst animal care facility (AAALAC certified) with a 12-hour light, 12-hour dark photoperiod and free access to tap water and a low-estrogen casein diet (Purina; Richmond, IN). After acclimation (3-5 days), gerbils are anesthetized with isoflurane (2-3% mixture with O₂), ovariectomized (Day 0). Beginning the following morning (Day 1), gerbils are treated subcutaneously each day with either vehicle (10% ETOH/corn oil), 17 β -estradiol (1 mg/kg, sc) or an experimental compound.. On Day 6, gerbils (n=4-5/group) are anesthetized with isoflurane, the common carotid arteries visualized via a mid-line neck incision and both arteries simultaneously occluded for 5 minutes with non-traumatic micro aneurysm clips. After occlusion, the clips are removed to allow cerebral reperfusion and the neck incision closed with wound clips. All animals are fasted overnight prior to

the global ischemia surgery, a step that facilitates consistent ischemic injury. On Day 12, gerbils are exposed to a lethal dose of CO₂, and the brains frozen on dry ice and stored at -80°C. The animal protocols used for these studies are reviewed and approved by the Radnor/Collegeville Animal Care and Use Committee (RACUC/CACUC) at Wyeth-Ayerst Research.

The degree of neuronal protection is evaluated by in situ hybridization analysis of neurogranin mRNA. Briefly, 20 µm coronal cryostat sections are collected on gelatin-coated slides, dried and stored at -80°C. At the time of processing, the desiccated slide boxes are warmed to room temperature, the slides postfixed in 4% paraformaldehyde, treated with acetic anhydride and then delipidated and dehydrated with chloroform and ethanol. Processed section-mounted slides are then hybridized with 200 µl (6x10⁶ DPM/ slide) of an antisense or sense (control) riboprobe for Neurogranin (³⁵S-UTP-labeled NG-241; bases 99-340). in a 50% formamide hybridization mix and incubated overnight at 55°C in a humidified slide chamber without coverslipping. The following morning, the slides are collected in racks, immersed in 2xSSC (0.3 M NaCl, 0.03 M sodium citrate; pH 7.0) / 10 mM DTT, treated with RNase A (20 µg/ml) and washed (2 x 30 min) at 67°C in 0.1x SSC to remove nonspecific label. After dehydration, the slides are opposed to BioMax (BMR-1; Kodak) X-ray film overnight.

The level of neurogranin hybridization signal is used to quantitatively assess the degree of neuronal loss in the CA1 region after injury and to evaluate the efficacy of 17β-estradiol and experimental compounds. Neurogranin mRNA is selected for these studies because it is highly expressed in the hippocampal neurons including CA1, but absent in glia and other cell types present in this brain region. Therefore, measurement of the amount of neurogranin mRNA present represents surviving neurons. Relative optical density measurements of neurogranin hybridization signal are obtained from film autoradiograms with a computer based image analysis system (C-Imaging Inc., Pittsburgh, PA). The results from 6 sections (40 µm apart) per animal are averaged and statistically evaluated. Numerical values are reported as the mean ± SEM. One-way analysis of variance is used to test for differences in the level of neurogranin mRNA and all statements of non-difference in the results section imply that p>0.05.

Middle cerebral artery occlusion in mice. Neuroprotection can be evaluated according to the test procedures described by Dubal [see, Dubal, et al., Proceedings of the National Academy of Sciences of the United States of America 98: 1952-1957 (2001), Dubal, et al., Journal of Neuroscience 19: 6385-6393 (1999)].

5

Ovulation inhibition standard pharmacological test procedure

The test procedure is used to determine whether test compounds can inhibit or change the timing of ovulation. It can also be used to determine the number of oocytes ovulated [Lundeen, et al., J Steroid Biochem Mol Biol 78: 137-143 (2001)].

10

Based on the results obtained in the standard pharmacological test procedures, the compounds of this invention are estrogen receptor modulators useful in the treatment or inhibition of conditions, disorders, or disease states that are at least partially mediated by an estrogen deficiency or excess, or which may be treated or inhibited through the use of an estrogenic agent. The compounds of this invention are particularly useful in treating a peri-menopausal, menopausal, or postmenopausal patient in which the levels of endogenous estrogens produced are greatly diminished. Menopause is generally defined as the last natural menstrual period and is characterized by the cessation of ovarian function, leading to the substantial diminution of circulating estrogen in the bloodstream. As used herein, menopause also includes conditions of decreased estrogen production that may be surgically, chemically, or be caused by a disease state which leads to premature diminution or cessation of ovarian function.

15

20

25

The compounds of this invention are also useful in inhibiting or treating other effects of estrogen deprivation including, hot flushes, vaginal or vulvar atrophy, atrophic vaginitis, vaginal dryness, pruritus, dyspareunia, dysuria, frequent urination, urinary incontinence, urinary tract infections. Other reproductive tract uses include the treatment or inhibition of dysfunctional uterine bleeding. The compounds are also useful in treating or inhibiting endometriosis.

30

The compounds of this invention are also active in the brain and are therefore useful for inhibiting or treating Alzheimer's disease, cognitive decline, decreased libido, senile dementia, neurodegenerative disorders, depression, anxiety, insomnia, schizophrenia, and infertility. The compounds of this invention are also useful in

treating or inhibiting benign or malignant abnormal tissue growth including, glomerulosclerosis, prostatic hypertrophy, uterine leiomyomas, breast cancer, scleroderma, fibromatosis, endometrial cancer, polycystic ovary syndrome, endometrial polyps, benign breast disease, adenomyosis, ovarian cancer, melanoma,
5 prostate cancer, cancers of the colon, CNS cancers, such as glioma or astioblastoma.

The compounds of this invention are cardioprotective and are antioxidants, and are useful in lowering cholesterol, triglycerides, Lp(a), and LDL levels; inhibiting or treating hypercholesteremia, hyperlipidemia, cardiovascular disease, atherosclerosis,
10 peripheral vascular disease, restenosis, and vasospasm, and inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage.

The compounds of this invention are also useful in treating disorders associated with inflammation or autoimmune diseases, including inflammatory bowel disease (Crohn's disease, ulcerative colitis, indeterminate colitis), arthritis (rheumatoid arthritis,
15 spondyloarthropathies, osteoarthritis), pleurisy, ischemia/reperfusion injury (e.g. stroke, transplant rejection, myocardial infarction, etc.), asthma, giant cell arteritis, prostatitis interstitial cystitis, uveitis, psoriasis, multiple sclerosis, systemic lupus erythematosus and sepsis.

The compounds of this invention are also useful in treating or inhibiting ocular
20 disorders including cataracts, uveitis, and macular degeneration and in treating skin conditions such as aging, alopecia, and acne.

The compounds of this invention are also useful in treating or inhibiting metabolic disorders such as type-II diabetes, of lipid metabolism, appetite (e.g. anorexia nervosa and bulimia).

25 Compounds in this invention are also useful in treating or inhibiting bleeding disorders such as hereditary hemorrhagic telangiectasia, dysfunctional uterine bleeding, and combating hemorrhagic shock.

The compounds of this invention are useful in disease states where amenorrhea is advantageous, such as leukemia, endometrial ablations, chronic renal
30 or hepatic disease or coagulation diseases or disorders.

The compounds of this invention can be used as a contraceptive agent, particularly when combined with a progestin.

When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that the effective dosage may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. Effective administration of the compounds of this invention may be given at an oral dose of from about 0.1 mg/day to about 1,000 mg/day. Preferably, administration will be from about 10 mg/day to about 600 mg/day, more preferably from about 50 mg/day to about 600 mg/day, in a single dose or in two or more divided doses. The projected daily dosages are expected to vary with route of administration.

Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parentally (including intravenous, intraperitoneal, intraarticularly and subcutaneous injections), rectally, intranasally, topically, ocularly (via eye drops), vaginally, and transdermally.

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying

agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time
5 release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

10 The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary
15 conditions of storage and use, these preparations contain a preservative to inhibit the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and
20 must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures
25 thereof, and vegetable oils.

For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically
30 acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic

absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

The preparation of representative examples of this invention is described below.

Intermediate 2

6-Methoxy-1-naphthol

A mixture of 6-methoxy-1-tetralone (20.84 g, 118.3 mmol), 10% Pd/C (10.1 g), and p-cymene (500 mL) was heated at reflux for 60 hours. The suspension was cooled to room temperature and filtered through Celite. The solid was washed with ethyl acetate until UV clear and the combined organic solution was extracted with 1N sodium hydroxide (3x 200 mL). The combined aqueous layers were made acidic with 6N HCl and extracted with ethyl acetate (3x 300 mL). The combined organic layers were dried over magnesium sulfate and filtered. Evaporation of the solvent and purification on a silica column (25% ethyl acetate-hexanes) yielded 17.02 g (83%) of the title compound as a light brown solid. An analytical sample was prepared by purification on a second silica column (40-60% dichloromethane-hexanes) to yield a white solid: mp 73-75°C; ¹H NMR (DMSO-d₆): δ 3.85 (3H, s), 6.70 – 6.74 (1H, m), 7.06 (1H, dd, *J* = 2.34 Hz, *J* = 9.15 Hz), 7.20 – 7.27 (3H, m), 8.02 (1H, d, *J* = 9.12 Hz), 10.01 (1H, s); MS (ESI) *m/z* 174 (M-H)⁺.

Anal. for $C_{11}H_{10}O_2$:

Calc'd: C: 75.84 H: 5.79

Found: C: 75.56 H: 5.39

5

Intermediate 5

1-[(2-bromo-5-methoxybenzyl)oxy]-6-methoxynaphthalene

To a solution of 6-methoxynaphthol (12.9 g, 74.1 mmol), 5-methoxy-2-bromobenzyl alcohol (17.7 g, 81.6 mmol), and triphenylphosphine (31.1 g, 119 mmol) in THF (400 mL) was slowly added a solution of DEAD (20.6 g, 119 mmol) in THF (50 mL). The solution was stirred overnight, concentrated onto silica, and purified by silica column (10% ethyl acetate – hexanes) to yield 16.38 g (59%) of the title compound as a white solid: mp 83-84°C; 1H NMR ($CDCl_3$): δ 3.78 (3H, s), 3.92 (3H, s), 5.25 (2H, s), 6.75 – 6.77 (2H, m), 7.12 (1H, d, J = 2.44 Hz), 7.15 (1H, dd, J = 2.44 Hz, J = 9.28 Hz), 7.24 (1H, d, J = 2.93 Hz), 7.32 – 7.36 (2H, m), 7.48 (1H, d, J = 8.79 Hz), 8.27 (1H, d, J = 9.23 Hz); MS (ESI) m/z 373/375 ($[M+H]^+$);

15

Anal. for $C_{19}H_{17}BrO_3$:

Calc'd: C: 61.14 H: 4.59

Found: C: 60.97 H: 4.49

20

Intermediate 6

1-[(2-bromo-5-methoxybenzyl)oxy]naphthalene

The title compound was prepared by reacting 1-naphthol (5.7 g, 39.6 mmol) with 5-methoxy-2-bromobenzyl alcohol as described for intermediate 5 to yield 5.94 g (44%) of a white solid: mp 74-75°C; 1H NMR ($CDCl_3$): δ 3.78 (3H, s), 5.28 (2H, s), 6.77 (1H, dd, J = 2.93 Hz, J = 8.79 Hz), 6.88 (1H, d, J = 7.69 Hz), 7.27 (1H, d, J = 3.30 Hz), 7.36 – 7.39 (1H, m), 7.47 – 7.53 (4H, m), 7.81 – 7.83 (1H, m), 8.37 – 8.39 (1H, m); MS (ESI) m/z 343/345 ($[M+H]^+$);

25

Anal. for $C_{18}H_{15}BrO_2$:

Calc'd: C: 62.99 H: 4.41

30

Found: C: 63.19 H: 4.30

Intermediate 8**4-bromo-2-fluoro-5-methylphenol**

To a solution of 2-fluoro-5-methylphenol (20.27 g, 160.7 mmol) in acetonitrile (500 mL) at 0°C was added NBS (30.0 g, 168.7 mmol). The mixture was stirred for 1
5 hour at 0°C. The resulting solution was stripped of solvent and filtered through a short silica column with dichloromethane to yield 29.6 g (90%) of an oily orange solid. An analytical sample was prepared by silica column purification (5% ethyl acetate – hexanes) to yield the title compound as a white solid: mp 44-46°C; ¹H NMR (DMSO-
d₆): δ 2.22 (3H, s), 6.93 (1H, d, *J* = 9.28 Hz), 7.40 (1H, d, *J* = 10.74 Hz), 10.05 (1H, s);
10 MS (ESI) *m/z* 203/205 ([M-H]⁻);

Anal. for C₇H₆BrFO:

Calc'd: C: 41.01 H: 2.95

Found: C: 40.69 H: 2.80

15

Intermediate 9**1-bromo-5-fluoro-4-methoxy-2-methylbenzene**

To a mixture of 4-bromo-2-fluoro-5-methylphenol (29.6 g, 144.2 mmol) and potassium carbonate (30.0 g, 218 mmol) in acetone (500 mL) was added iodomethane (69.0 g, 486 mmol). The resulting suspension was stirred at reflux for 4
20 hours. The reaction mixture was cooled to RT, poured into HCl (250 mL of 1N solution) and extracted with ethyl acetate (3x 250 mL). The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate and filtered. Evaporation of the solvent and purification on a silica column (5% ethyl acetate – hexanes) yielded 29.50 g (93%) of the title compound as a clear, colorless oil: ¹H
25 NMR (CDCl₃): δ 2.33 (3H, s), 3.85 (3H, s), 6.82 (1H, d, *J* = 8.79 Hz), 7.23 (1H, d, *J* = 10.25 Hz); MS *m/z*;

Anal. for C₈H₈BrFO · 0.3 H₂O:

Calc'd: C: 42.81 H: 3.86

Found: C: 42.38 H: 3.44

30

Intermediate 11**1-[(2-Bromo-4-fluoro-5-methoxybenzyl)oxy]-6-methoxynaphthalene**

A mixture of 1-bromo-5-fluoro-4-methoxy-2-methylbenzene (29.50 g, 134.7 mmol), NBS (25.18 g, 141.4 mmol) and benzoyl peroxide (8.14 g, 33.7 mmol) in

carbon tetrachloride (500 mL) was stirred at reflux for 1 hour. The reaction was cooled to room temperature and filtered through silica with dichloromethane. Evaporation of the solvent yielded the benzyl bromide intermediate. This light yellow solid was combined with 6-methoxy-1-naphthol (23.4 g, 134.7 mmol), and potassium carbonate (37.2 g, 269 mmol) in acetone (500 mL) and stirred at reflux for 12 hours. The cooled reaction mixture was filtered through silica with acetone, stripped of solvent, and purified by silica column chromatography (10% - 30% ethyl acetate – hexanes) followed by trituration with ethyl acetate to yield 20.3 g (39%) of the title compound as a white solid: mp 138-142 °C; ¹H NMR (CDCl₃): δ 3.85 (3H, s), 3.92 (3H, s), 5.22 (2H, s), 7.75 (1H, dd, *J* = 2.07 Hz, *J* = 6.50 Hz), 7.12 – 7.17 (2H, m), 7.25 – 7.38 (4H, m), 8.22 (1H, d, *J* = 8.80 Hz); MS (ESI) *m/z* 391/393 ([M+H]⁺);

Anal. for C₁₉H₁₆BrFO₃:

Calc'd: C: 58.33 H: 4.12

Found: C: 58.15 H: 3.98

Intermediate 12

2,8-Dimethoxy-6*H*-dibenzo[*c,h*]chromene

Method A

A mixture of 1-[(2-bromo-5-methoxybenzyl)oxy]-6-methoxynaphthalene (13.03 g, 34.93 mmol), sodium acetate (10.3 g, 105 mmol), and dichlorobis(triphenylphosphine)-palladium(II) (3.68 g, 5.25 mmol) in DMA (600 mL) was stirred 12 hours at 120 °C. The cooled reaction mixture was poured into 1500 mL water. The crude solid product was collected by filtration and purified by silica chromatography (5% - 10% ethyl acetate – hexanes) to yield 5.76 g (56%) of the title compound as a white solid: mp 175-178 °C; ¹H NMR (CDCl₃): δ 3.85 (3H, s), 3.92 (3H, s), 5.25 (2H, s), 6.75 (1H, d, *J* = 2.20 Hz), 6.93 (1H, dd, *J* = 2.56 Hz, *J* = 8.42 Hz), 7.10 (1H, d, *J* = 2.56 Hz), 7.13 (1H, dd, *J* = 2.56 Hz, *J* = 9.15 Hz), 7.41 (1H, d, *J* = 8.79 Hz), 7.63 (1H, d, *J* = 8.42 Hz), 7.74 (1H, d, *J* = 8.79 Hz), 8.14 (1H, d, *J* = 9.15 Hz); MS (ESI) *m/z* 293 ([M+H]⁺);

Anal. for C₁₉H₁₆O₃:

Calc'd: C: 78.06 H: 5.52

Found: C: 78.01 H: 5.41

Intermediate 13**8-Methoxy-6*H*-dibenzo[*c,h*]chromene**

The title compound was prepared by reacting 1-[(2-bromo-5-methoxybenzyl)-oxy]naphthalene (3.05 g, 8.89 mmol) according to method A to yield 0.94 g (40%) of a white solid: mp 128-130°C; ¹H NMR (DMSO-*d*₆): δ 3.82 (3H, s), 5.31 (2H, s), 6.96 – 7.02 (2H, m), 7.47 – 7.53 (2H, m), 7.60 (1H, d, *J* = 8.55 Hz), 7.82 (1H, d, *J* = 8.48 Hz), 7.86 – 7.91 (1H, m), 7.94 (1H, d, *J* = 8.65 Hz), 8.12 – 8.15 (1H, m); MS (ESI) *m/z* 263 ([*M*+*H*]⁺);

Anal. for C₁₈H₁₄O₂:

Calc'd: C: 82.42 H: 5.38

Found: C: 81.98 H: 5.07

Intermediate 14**9-Fluoro-2,8-dimethoxy-6*H*-dibenzo[*c,h*]chromene**

The title compound was prepared by reacting 1-[(2-bromo-4-fluoro-5-methoxybenzyl)oxy]-6-methoxynaphthalene (10.3 g, 26.3 mmol) according to method A to yield 4.51 g (55%) of a white solid: mp 201-206°C; ¹H NMR (CDCl₃): δ 3.93 (3H, s), 3.94 (3H, s), 5.23 (2H, s), 6.84 (1H, d, *J* = 8.24 Hz), 7.11 – 7.13 (2H, m), 7.40 – 7.443 (2H, m), 7.64 (1H, d, *J* = 8.60 Hz), 8.11 – 8.13 (1H, m); MS (ESI) *m/z* 311 ([*M*+*H*]⁺);

Anal. for C₁₉H₁₅FO₃:

Calc'd: C: 73.54 H: 4.87

Found: C: 73.84 H: 4.60

Example 1a**6*H*-Dibenzo[*c,h*]chromene-2,8-diol****Method D**

To pyridinium HCl (11g) at 190°C was added 2,8-dimethoxy-*H*-dibenzo[*c,h*]-chromene (2.48 g, 8.49 mmol). The resulting solution was stirred at 190°C for 3 hours. The reaction was cooled to room temperature and taken up in water (400 mL). The solid product was collected by filtration and purified on a silica column to yield 2.09 g (93%) of a light yellow solid. This material was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 248-252°C(d);

¹H NMR (DMSO-d₆): δ 5.19 (2H, s), 6.70 (1H, d, *J* = 2.44 Hz), 6.80 (1H, dd, *J* = 2.44 Hz, *J* = 8.30 Hz), 7.04 (1H, dd, *J* = 2.44 Hz, *J* = 8.79 Hz), 7.08 (1H, d, *J* = 2.44 Hz), 7.34 (1H, d, *J* = 8.79 Hz), 7.62 (1H, d, *J* = 8.30 Hz), 7.76 (1H, d, *J* = 8.79 Hz), 7.96 (1H, d, *J* = 9.28 Hz), 9.63 (1H, s), 9.78 (1H, s); MS (ESI) *m/z* 265 ([M+H]⁺); MS (ESI)

5 *m/z* 263 ([M-H]⁻);

Anal. for C₁₇H₁₂O₃ · 0.1 H₂O:

Calc'd: C: 76.74 H: 4.62

Found: C: 76.57 H: 4.25

10

Example 1b

9-Fluoro-6*H*-dibenzo[*c,h*]chromene-2,8-diol

The title compound was prepared by reacting 9-fluoro-2,8-dimethoxy-*H*-dibenzo[*c,h*]chromene (1.29 g, 4.16 mmol) with pyridinium HCl (30 g) according to method D to yield 1.01 g (86%) of a tan solid. This material was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 230-231°C(dec); ¹H NMR (DMSO-d₆): δ 5.19 (2H, s), 6.89 (1H, d, *J* = 8.73 Hz), 7.04 – 7.10 (2H, m), 7.35 (1H, d, *J* = 8.65 Hz), 7.64 (1H, d, *J* = 12.48 Hz), 7.77 (1H, d, *J* = 8.75 Hz), 7.97 (1H, d, *J* = 8.90 Hz), 9.89 (1H, bs), 10.01 (1H, bs); MS (ESI) *m/z* 283 ([M+H]⁺); MS (ESI) *m/z* 281 ([M-H]⁻);

20

Anal. for C₁₇H₁₁FO₃ · 0.75 H₂O:

Calc'd: C: 69.03 H: 4.26

Found: C: 69.34 H: 3.70

Example 1c

25

6*H*-Dibenzo[*c,h*]chromen-8-ol

Method D

The title compound was prepared by reacting 8-methoxy-*H*-dibenzo[*c,h*]chromene (0.73 g, 2.79 mmol) with pyridinium HCl (10 g) according to method D to yield 0.63 g (91%) of a white solid: mp 192-194°C; ¹H NMR (DMSO-d₆): δ 5.25 (2H, s), 6.73 (1H, bs), 6.83 (1H, dd, *J* = 2.38 Hz, *J* = 8.40 Hz), 7.45 – 7.52 (2H, m), 7.58 (1H, d, *J* = 8.58 Hz), 7.70 (1H, d, *J* = 8.34 Hz), 7.84 – 7.93 (2H, m), 8.10 – 8.12 (1H, m), 9.73 (1H, s); MS (ESI) *m/z* 247 ([M-H]⁻);

30

Anal. for $C_{17}H_{12}O_2$:

Calc'd: C: 82.24 H: 4.87

Found: C: 81.85 H: 4.86

5

Intermediate 15

12-Bromo-2,8-dimethoxy-6*H*-dibenzo[*c,h*]chromene

Method B

To a mixture of 2,8-dimethoxy-*H*-dibenzo[*c,h*]chromene (1.97 g, 6.75 mmol) in acetonitrile (70 mL) at °C was added NBS (1.44 g, 8.10 mmol). The mixture was stirred at 0°C for 15 minutes, poured into 300 mL water and extracted with ethyl acetate (3x 150 mL). The combined organic layers were washed with water, dried over sodium sulfate and filtered. Evaporation of the solvent and purification by silica chromatography yielded a white solid which was recrystallized from 50 mL of isopropanol to yield 1.77 g (71%) of the title compound as a white crystalline solid:

10 mp 96-98 °C; 1H NMR ($CDCl_3$): δ 3.86 (3H, s), 3.98 (3H, s), 5.24 (2H, s), 6.74 (1H, d, $J = 2.444$ Hz), 6.93 (1H, dd, $J = 2.68$ Hz, $J = 8.54$ Hz), 7.15 (1H, dd, $J = 2.44$ Hz, $J = 9.28$ Hz), 7.43 (1H, d, $J = 2.41$ Hz), 7.59 (1H, d, $J = 8.79$ Hz), 8.04 (1H, s), 8.16 (1H, d, $J = 9.28$ Hz); MS m/z ;

Anal. for $C_{19}H_{15}BrO_3$:

20 Calc'd: C: 61.47 H: 4.07

Found: C: 61.66 H: 3.89

Intermediate 16

12-Bromo-9-fluoro-2,8-dimethoxy-6*H*-dibenzo[*c,h*]chromene

25 The title compound was prepared by reacting 9-fluoro-2,8-dimethoxy-*H*-dibenzo[*c,h*]chromene (1.47 g, 4.74 mmol) with NBS (1.01 g, 5.69 mmol) according to method B to yield 1.14 g (62%) of a tan solid: mp 139-143 °C; 1H NMR ($CDCl_3$): δ 3.98 (3H, s), 3.98 (3H, s), 5.22 (2H, s), 6.78 (1H, d, $J = 8.24$ Hz), 7.16 (1H, dd, $J = 2.56$ Hz, $J = 9.15$ Hz), 7.37 (1H, d, $J = 12.08$ Hz), 7.43 (1H, d, $J = 2.56$ Hz), 7.92 (1H, s), 8.14 (1H, dd, $J = 0.37$ Hz, $J = 9.15$ Hz); MS (ESI) m/z 387/389 ($[M+H]^+$);

30

Anal. for $C_{19}H_{14}BrFO_3$:

Calc'd: C: 58.63 H: 3.63

Found: C: 58.82 H: 3.58

Intermediate 17**2,8-Dimethoxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile****Method C**

5 A mixture of 12-bromo-2,8-dimethoxy-*H*-dibenzo[*c,h*]chromene (8.33 g, 22.45 mmol), zinc cyanide (3.15 g, 26.9 mmol), and tetrakis(triphenylphosphine)palladium(0) (1.30 g, 1.12 mmol) in DMF (100 mL) was stirred at 120°C overnight. The cooled reaction mixture was poured into ammonium chloride solution (600 mL of 1N solution) and extracted with ethyl acetate (4x 300 mL). The combined organic layers were
10 washed with ammonium chloride solution, filtered through a silica plug, stripped of solvent, and purified on a silica column (40% – 60% dichloromethane – hexanes) to yield a yellow solid. This solid was triturated with ethyl acetate to yield 5.43 g (76%) of the title compound as a yellow solid: mp 161-165°C; ¹H NMR (CDCl₃): δ 3.86 (3H, s), 3.98 (3H, s), 5.32 (2H, s), 6.73 (1H, d, *J* = 2.56 Hz), 6.96 (1H, dd, *J* = 2.56 Hz, *J* =
15 8.42 Hz), 7.19 (1H, dd, *J* = 2.56 Hz, *J* = 9.15 Hz), 7.37 (1H, d, *J* = 2.20 Hz), 7.60 (1H, d, *J* = 8.42 Hz), 8.16 (1H, s), 8.18 (1H, d, *J* = 9.52 Hz); MS (ESI) *m/z* 317 ([*M*+H]⁺);

Anal. for C₂₀H₁₅NO₃:

Calc'd: C: 75.70 H: 4.76 N: 4.41

Found: C: 75.53 H: 4.48 N: 4.32

20

Intermediate 18**9-Fluoro-2,8-dimethoxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile**

The title compound was prepared by reacting 9-fluoro-2,8-dimethoxy-*H*-dibenzo[*c,h*]chromene (0.99 g, 2.55 mmol) with zinc cyanide (0.45 g, 3.8 mmol)
25 according to method C to yield 0.55 g (64%) of a white solid: mp > 220°C; ¹H NMR (CDCl₃): δ 3.92 (3H, s), 3.97 (3H, s), 5.29 (2H, s), 6.77 (1H, d, *J* = 8.05 Hz), 7.19 (1H, dd, *J* = 2.47 Hz, *J* = 9.24 Hz), 7.36 – 7.39 (2H, m), 8.04 (1H, s), 8.17 (1H, d, *J* = 9.15 Hz); MS *m/z*;

Anal. for C₂₀H₁₄FNO₃ · 0.1 H₂O:

30 Calc'd: C: 71.25 H: 4.25 N: 4.16

Found: C: 70.87 H: 3.91 N: 4.31.

Example 1d**2,8-Dihydroxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile**

The title compound was prepared by reacting 2,8-dimethoxy-*H*-dibenzo[*c,h*]-chromene-12-carbonitrile (5.43 g, 17.1 mmol) with pyridinium HCl (50 g) according to Method D to afford 3.43 g (69%) of a yellow solid: mp > 250 °C; ¹H NMR (DMSO-*d*₆): δ 5.34 (2H, s), 6.71 (1H, d, *J* = 2.36 Hz), 6.82 (1H, dd, *J* = 2.48 Hz, *J* = 8.41 Hz), 7.19 (1H, dd, *J* = 2.32 Hz, *J* = 9.11 Hz), 7.30 (1H, d, *J* = 2.26 Hz), 7.78 (1H, d, *J* = 8.56 Hz), 8.11 (1H, d, *J* = 9.14 Hz), 8.50 (1H, s), 9.81 (1H, s), 10.46 (1H, bs); MS (ESI) *m/z* 288 ([M-H]⁻);

Anal. for C₁₈H₁₁NO₃ · 0.25 H₂O:
Calc'd: C: 73.59 H: 3.95 N: 4.77
Found: C: 73.69 H: 3.84 N: 4.53.

Example 1e**9-fluoro-2,8-dihydroxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile**

The title compound was prepared by reacting 9-fluoro-2,8-dimethoxy-*H*-dibenzo[*c,h*]chromene-12-carbonitrile (0.40 g, 1.19 mmol) with pyridinium HCl (15 g) according to method D to yield 0.32 g (88%) of a white solid: mp > 250°C; ¹H NMR (DMSO-*d*₆): δ 5.29 (2H, s), 6.86 (1H, d, *J* = 8.69 Hz), 7.16 (1H, dd, *J* = 2.32 Hz, *J* = 9.15 Hz), 7.28 (1H, d, *J* = 2.32 Hz), 7.80 (1H, d, *J* = 12.40 Hz), 8.08 (1H, d, *J* = 9.04 Hz), 8.49 (1H, s), 10.16 (1H, s), 10.4 (1H, s); MS (ESI) *m/z* 306 ([M-H]⁻);

Anal. for C₁₈H₁₀FNO₃ · 0.3 H₂O:
Calc'd: C: 69.14 H: 3.42 N: 4.48
Found: C: 68.91 H: 3.10 N: 4.30.

Example 1f**1-Chloro-2,8-dihydroxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile**

The title compound was prepared by reacting 2,8-dihydroxy-*H*-dibenzo[*c,h*]-chromene-12-carbonitrile (0.20 g, 0.70 mmol) with NCS (0.11 g, 0.83 mmol) in THF (10 mL) at room temperature overnight according to method B to yield 0.10 g (45 %) of a yellow solid: mp > 250°C; ¹H NMR (DMSO-*d*₆): δ 5.34 (2H, s), 6.72 (1H, d, *J* = 2.35 Hz), 6.83 (1H, dd, *J* = 2.43 Hz, *J* = 8.44 Hz), 7.37 (1H, d, *J* = 9.22 Hz), 7.84

(1H, d, J = 8.57 Hz), 8.14 (1H, d, J = 9.20 Hz), 8.53 (1H, s), 9.87 (1H, bs), 1.12 (1H, bs); MS (ESI) m/z 322/324 ([M-H]⁻);

Anal. for C₁₈H₁₀ClNO₃ · 0.75 H₂O:

Cal'd: C: 64.11 H: 3.44 N: 4.33

5 Found: C: 64.45 H: 3.05 N: 4.03.

Example 1g

1-Chloro-6*H*-dibenzo[*c,h*]chromene-2,8-diol

The title compound was prepared by reacting *H*-dibenzo[*c,h*]chromene-2,8-diol
10 (0.218 g, 0.83 mmol) with NCS (0.13 g, 0.99 mmol) in THF (10 mL) according to method B to yield 0.17 g (67%) of the title compound along with 0.025 g (10%) of the 12-chloro-*H*-dibenzo[*c,h*]chromene-2,8-diol isomer. These isomers were separated by preparative HPLC. mp 216-218 °C; ¹H NMR (DMSO-*d*₆): δ 5.24 (2H, s), 6.72 (1H, d, J = 2.29 Hz), 6.82 (1H, dd, J = 2.40 Hz, J = 8.39 Hz), 7.25 (1H, d, J = 9.11 Hz),
15 7.67 (2H, d, J = 8.69 Hz), 7.94 – 7.99 (2H, m), 9.72 (1H, bs), 10.50 (1H, bs); MS (ESI) m/z 297/299 ([M-H]⁻);

Anal. for C₁₇H₁₁ClO₃ · 0.25 H₂O:

Calc'd: C: 67.34 H: 3.82

Found: C: 67.25 H: 3.89

20

Intermediate 19

2-(Acetyloxy)-6*H*-dibenzo[*c,h*]chromen-8-yl acetate

Method E

A mixture of *H*-dibenzo[*c,h*]chromene-2,8-diol (1.82 g, 6.49 mmol), pyridine (25
25 mL) and acetic anhydride (25mL) was stirred overnight at room temperature and poured into water (300 mL). The white solid product was collected by filtration, washed with water, and dried under vacuum at 105°C to yield 2.11 g (88%) of the title compound as a white solid: mp 172-173°C; ¹H NMR (DMSO-*d*₆): δ 2.31 (3H, s), 2.34 (3H, s), 5.36 (2H, s), 7.17 (1H, d, J = 2.44 Hz), 7.21 (1H, dd, J = 2.43 Hz, J = 8.29
30 Hz), 7.21 (1H, dd, J = 2.44 Hz, J = 9.28 Hz), 7.63 (1H, d, J = 8.30 Hz), 7.68 (1H, d, J = 2.44 Hz), 7.94 (1H, d, J = 8.30 Hz), 8.04 (1H, d, J = 8.79 Hz), 8.18 (1H, d, J = 9.28 Hz); MS (ESI) m/z 349 ([M+H]⁺);

Anal. for $C_{21}H_{16}O_5$:

Calc'd: C: 72.41 H: 4.63

Found: C: 72.20 H: 4.67

5

Intermediate 20

2-(Acetyloxy)-9-fluoro-6*H*-dibenzo[*c,h*]chromen-8-yl acetate

The title compound was prepared by reacting 9-fluoro-*H*-dibenzo[*c,h*]-chromene-2,8-diol (0.84 g, 2.98 mmol) with pyridine (10 mL) and acetic anhydride (10 mL) according to method E to yield 0.93 g (86%) of a white solid: mp 206-212°C; 1H NMR (DMSO- d_6): δ 2.30 (3H, s), 2.33 (3H, s), 5.30 (2H, s), 7.28 – 7.32 (2H, m), 7.59 (1H, d, J = 8.61 Hz), 7.64 (1H, d, J = 2.38 Hz), 7.92 (1H, d, J = 11.54 Hz), 8.01 (1H, d, J = 8.79 Hz), 8.15 (1H, d, J = 9.16 Hz); MS (ESI) m/z 367 ($[M+H]^+$);

Anal. for $C_{21}H_{15}FO_5$:

Calc'd: C: 68.85 H: 4.13

15

Found: C: 68.41 H: 4.06

Intermediate 21

2-(Acetyloxy)-12-bromo-6*H*-dibenzo[*c,h*]chromen-8-yl acetate

The title compound was prepared by reacting 2-(acetyloxy)-*H*-dibenzo[*c,h*]-chromen-8-yl acetate (1.63 g, 4.68 mmol) with NBS (1.00 g, 5.62 mmol) in acetonitrile (100 mL) at room temperature overnight according to method B to yield 2.00 g (quantitative yield) of a white solid: mp 192-194°C; 1H NMR ($CDCl_3$): δ 2.33 (3H, s), 2.38 (3H, s), 5.28 (2H, s), 6.99 (1H, d, J = 2.20 Hz), 7.14 (1H, dd, J = 2.34 Hz, J = 8.42 Hz), 7.29 (1H, dd, J = 2.26 Hz, J = 9.11 Hz), 7.69 (1H, d, J = 8.47 Hz), 7.86 (1H, d, J = 2.17 Hz), 8.09 (1H, s), 8.28 (1H, d, J = 9.05 Hz); MS m/z ;

Anal. for $C_{21}H_{15}BrO_5$:

Calc'd: C: 59.04 H: 3.54

Found: C: 58.95 H: 3.43

30

Intermediate 22

2-(Acetyloxy)-12-chloro-6*H*-dibenzo[*c,h*]chromen-8-yl acetate

The title compound was prepared by reacting 2-(acetyloxy)-*H*-dibenzo[*c,h*]-chromen-8-yl acetate (0.26 g, 0.75 mmol) with NCS (0.12 g, 0.90 mmol) in acetonitrile

(10 mL) at reflux for 3 hours according to method B to yield 0.24 g (84%) of a white solid: mp 183-184°C; ¹H NMR (CDCl₃): δ 2.33 (3H, s), 2.38 (3H, s), 5.28 (2H, s), 6.99 (1H, d, *J* = 2.27 Hz), 7.14 (1H, dd, *J* = 2.34 Hz, *J* = 8.42 Hz), 7.30 (1H, dd, *J* = 2.27 Hz, *J* = 9.07 Hz), 7.68 (1H, d, *J* = 8.49 Hz), 7.88 – 7.89 (2H, m), 8.29 (1H, d, *J* = 9.06 Hz); MS *m/z*;

Anal. for C₂₁H₁₅ClO₅ · 0.1 H₂O:

Calc'd: C: 65.58 H: 3.98

Found: C: 65.37 H: 3.55

10

Intermediate 23

2-(Acetyloxy)-12-bromo-9-fluoro-6*H*-dibenzo[*c,h*]chromen-8-yl acetate

The title compound was prepared by reacting 2-(acetyloxy)-9-fluoro-*H*-dibenzo[*c,h*]chromen-8-yl acetate (0.47 g, 1.28 mmol) with NBS (0.27 g, 1.54 mmol) in acetonitrile (25 mL) at room temperature overnight according to method B to yield 0.57 g (quantitative yield) of a white solid. An analytical sample was obtained by trituration with ethyl acetate to yield the title compound as a white solid: mp 190-193°C; ¹H NMR (DMSO-*d*₆): δ 2.36 (3H, s), 2.37 (3H, s), 5.34 (2H, s), 7.34 (1H, d, *J* = 7.69 Hz), 7.46 (1H, dd, *J* = 2.23 Hz, *J* = 9.05 Hz), 7.81 (1H, d, *J* = 2.18 Hz), 8.09 (1H, d, *J* = 11.65 Hz), 8.28 (1H, d, *J* = 9.08 Hz), 8.47 (1H, s); MS (ESI) *m/z* 462/464 ([*M*+NH₄]⁺);

20

Anal. for C₂₁H₁₄BrFO₅:

Calc'd: C: 56.65 H: 3.17

Found: C: 56.59 H: 3.16

25

Intermediate 24

2-(Acetyloxy)-12-chloro-9-fluoro-6*H*-dibenzo[*c,h*]chromen-8-yl acetate

The title compound was prepared by reacting 2-(acetyloxy)-9-fluoro-*H*-dibenzo[*c,h*]chromen-8-yl acetate (0.47 g, 0.1.28 mmol) with NCS (0.21 g, 1.54 mmol) in acetonitrile (15 mL) at reflux for 4 hours according to method B to yield 0.55 g (quantitative yield) of a yellow solid. An analytical sample was obtained by trituration with ethyl acetate to yield the title compound as a white solid mp 194-198 °C; ¹H NMR (DMSO-*d*₆): δ 2.36 (3H, s), 2.37 (3H, s), 5.37 (2H, s), 7.34 (1H, d, *J* = 7.66 Hz), 7.48

30

(1H, dd, $J = 2.16$ Hz, $J = 9.06$ Hz), 7.85 (1H, d, $J = 2.07$ Hz), 8.08 (1H, d, $J = 11.61$ Hz), 8.28 (1H, d, $J = 9.10$ Hz), 8.32 (1H, s); MS (ESI) m/z 399/401 ([M-H]⁻);

Anal. for C₂₁H₁₄ClFO₅:

Calc'd: C: 62.93 H: 3.52

5 Found: C: 62.53 H: 3.53

Example 1h

12-Bromo-6*H*-dibenzo[*c,h*]chromene-2,8-diol

Method F

10 A solution of 2-(acetyloxy)-12-bromo-*H*-dibenzo[*c,h*]chromen-8-yl acetate (1.40 g, 3.28 mmol) in sodium methoxide (40 mL of 1N in methanol) was stirred at room temperature for 2 hours. The solution was poured into 100 mL 1N HCl and extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed with sodium bicarbonate solution, washed with brine, dried over sodium sulfate and
15 filtered. Evaporation of the solvent and purification by silica chromatography (40% ethyl acetate – hexanes) yielded 0.91 g (81%) of the title compound as a white solid: mp 178-180(decomposes), discolors above 160 °C; ¹H NMR (DMSO-*d*₆): δ 5.23 (2H, s), 6.71 (1H, d, $J = 2.32$ Hz), 6.80 (1H, dd, $J = 2.43$ Hz, $J = 8.39$ Hz), 7.12 (1H, dd, $J = 2.32$ Hz, $J = 9.03$ Hz), 7.34 (1H, d, $J = 2.28$ Hz), 7.58 (1H, d, $J = 8.53$ Hz), 8.04 (1H,
20 d, $J = 9.07$ Hz), 8.14 (1H, s), 9.73 (1H, bs), 10.20 (1H, bs); MS (ESI) m/z 341/343 ([M-H]⁻);

Anal. for C₁₇H₁₁BrO₃:

Calc'd: C: 59.50 H: 3.23

Found: C: 59.33 H: 3.26

25

Example 1i

12-Chloro-6*H*-dibenzo[*c,h*]chromene-2,8-diol

The title compound was prepared by reacting 2-(acetyloxy)-12-chloro-*H*-dibenzo[*c,h*]chromen-8-yl acetate (0.18 g, 0.47 mmol) with sodium methoxide solution
30 (75 mL of 1N in methanol) according to method F to yield 0.13 g (93%) of a tan solid. This material was further purified by reverse phase preparative HPLC to yield a the title compound as a light pink solid: mp 212-216 °C(d); ¹H NMR (DMSO-*d*₆): δ 5.23 (2H, s), 6.71 (1H, d, $J = 2.33$ Hz), 6.80 (1H, dd, $J = 2.44$ Hz, $J = 8.39$ Hz), 7.14 (1H, dd, $J = 2.34$ Hz, $J = 9.09$ Hz), 7.35 (1H, d, $J = 2.31$ Hz), 7.68 (1H, d, $J = 8.54$ Hz),

7.98 (1H, s), 8.05 (1H, d, $J = 9.07$ Hz), 9.74 (1H, bs), 10.19 (1H, bs); MS (ESI) m/z 299/301 ($[M+H]^+$); MS (ESI) m/z 297/299 ($[M-H]^-$);

Anal. for $C_{17}H_{11}ClO_3 \cdot 0.1 H_2O$:

Calc'd: C: 67.94 H: 3.76

5 Found: C: 67.77 H: 3.67

Example 1j

12-Bromo-9-fluoro-6H-dibenzo[c,h]chromene-2,8-diol

The title compound was prepared by reacting 2-(acetyloxy)-12-bromo-9-fluoro-
10 *H*-dibenzo[c,h]chromen-8-yl acetate (0.48 g, 1.08 mmol) with sodium methoxide solution (40 mL of 1N in methanol) according to method F. Purification by reverse phase preparative HPLC yielded 0.20 g (53%) of the title compound as a white solid: mp 194-197°C; 1H NMR (DMSO- d_6): δ 5.22 (2H, s), 6.89 (1H, d, $J = 8.68$ Hz), 7.13 (1H, dd, $J = 2.31$ Hz, $J = 9.05$ Hz), 7.35 (1H, d, $J = 2.27$ Hz), 7.75 (1H, D, $J = 12.46$
15 Hz), 8.04 (1H, d, $J = 9.06$ Hz), 8.19 (1H, s), 10.21 (2H, bs); MS (ESI) m/z 359/361 ($[M-H]^-$);

Anal. for $C_{17}H_{10}BrFO_3 \cdot 0.75 H_2O$:

Calc'd: C: 54.50 H: 3.09

Found: C: 54.85 H: 2.89

20

Example 1k

12-Chloro-9-fluoro-6H-dibenzo[c,h]chromene-2,8-diol

The title compound was prepared by reacting 2-(acetyloxy)-12-chloro-9-fluoro-
25 *H*-dibenzo[c,h]chromen-8-yl acetate (0.44 g, 1.10 mmol) with sodium methoxide solution (40 mL of 1N in methanol) according to method F to yield 0.30 g (86%) of a tan solid. This material was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 215-220 °C (dec); 1H NMR (DMSO- d_6): δ 5.22 (2H, s), 6.89 (1H, d, $J = 8.68$ Hz), 7.15 (1H, dd, $J = 2.22$ Hz, $J = 9.05$ Hz), 7.35 (1H, d, $J = 2.13$ Hz), 7.74 (1H, d, $J = 12.42$ Hz), 8.03 – 8.06 (2H, m), 10.21 (2H,
30 bs); MS (ESI) m/z 315/317 ($[M-H]^-$);

Anal. for $C_{17}H_{10}ClFO_3 \cdot 0.25 H_2O$:

Calc'd: C: 63.57 H: 3.29

Found: C: 63.22 H: 3.27

Example 11**12-Methoxy-6*H*-dibenzo[*c,h*]chromene-2,8-diol**

A mixture of 2-(acetyloxy)-12-methoxy-*H*-dibenzo[*c,h*]chromen-8-yl acetate
5 (2.06 g, 6.00 mmol), CuBr (0.86 g, 6.00 mmol), sodium methoxide (15 mL of 25% in methanol), and DMF (30 mL) was heated at reflux for 3 hours. The reaction was cooled to room temperature, poured into HCl solution (200 mL of 2 N), and extracted with ethyl acetate (3x 250 mL). The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate and filtered. Evaporation of
10 the solvent and purification by silica column chromatography (40% ethyl acetate – hexanes) yielded 1.11 g (63 %) of the title compound as a tan solid: mp 224 °C(d); ¹H NMR (DMSO-*d*₆): δ 3.98 (3H, s), 5.12 (2H, s), 6.70 (1H, d, *J* = 2.47 Hz), 6.81 (1H, dd, *J* = 2.47 Hz, *J* = 8.24 Hz), 7.05 (1H, dd, *J* = 2.47 Hz, *J* = 9.06 Hz), 7.18 (1H, s), 7.35 (1H, d, *J* = 2.47 Hz), 7.68 (1H, d, *J* = 8.51 Hz), 7.92 (1H, d, *J* = 9.06 Hz), 9.63 (1H, s),
15 9.80 (1H, s); MS (ESI) *m/z* 293 ([M-H]⁻); MS (ESI) *m/z* 295 ([M+H]⁺);

Anal. for C₁₈H₁₄O₄ · 0.3 H₂O:

Calc'd: C: 72.14 H: 4.90

Found: C: 71.88 H: 4.74

20

Intermediate 25**2-(Acetyloxy)-12-methoxy-6*H*-dibenzo[*c,h*]chromen-8-yl acetate**

The title compound was prepared by reacting 12-methoxy-*H*-dibenzo[*c,h*]chromene-2,8-diol (1.11 g, 3.78 mmol) with pyridine and acetic anhydride according to method E to yield 1.11 g (78%) of a light yellow solid: mp 126-134°C; ¹H NMR
25 (DMSO-*d*₆): δ 2.31 (3H, s), 2.33 (3H, s), 4.05 (3H, s), 5.28 (2H, s), 7.16 (1H, d, *J* = 2.32 Hz), 7.22 (1H, dd, *J* = 2.44 Hz, *J* = 8.34 Hz), 7.35 (1H, dd, *J* = 2.32 Hz, *J* = 9.04 Hz), 7.42 (1H, s), 7.80 (1H, m), 8.01 (1H, d, *J* = 8.58 Hz), 8.14 (1H, dd, *J* = 0.35 Hz, *J* = 9.04 Hz);

Anal. for C₂₂H₁₈O₆ · 0.25 H₂O:

30

Calc'd: C: 69.01 H: 4.87

Found: C: 69.08 H: 4.88

Example 1m**11-Chloro-12-methoxy-6H-dibenzo[c,h]chromene-2,8-diol**

The title compound was prepared by reacting 2-(acetyloxy)-12-methoxy-*H*-dibenzo[c,h]chromen-8-yl acetate (0.41 g, 1.08 mmol) with NCS (0.17 g, 1.30 mmol) in acetonitrile (10 mL) according to method B followed by deacylation according to method F to yield 0.050 g (14%) of a pink solid: mp discolors > 230°C; ¹H NMR (DMSO-d₆): δ 3.87 (3H, s), 5.06 (2H, s), 6.80 (1H, d, *J* = 2.35 Hz), 6.84 (1H, dd, *J* = 2.55 Hz, *J* = 8.63 Hz), 7.11 (1H, dd, *J* = 2.34 Hz, *J* = 9.06 Hz), 7.23 (1H, d, *J* = 2.30 Hz), 8.01 (1H, d, *J* = 9.05 Hz), 8.11 (1H, d, *J* = 8.60 Hz), 9.81 (1H, bs), 10.14 (1H, bs); MS (ESI) *m/z* 329/331 ([M+H]⁺); MS (ESI) *m/z* 327/329 ([M-H]⁻);

Anal. for C₁₈H₁₃ClO₄ · 0.25 H₂O:

Calc'd: C: 64.87 H: 4.08

Found: C: 64.90 H: 4.09

Example 1n**12-Methyl-6H-dibenzo[c,h]chromene-2,8-diol**

A mixture of 12-bromo-*H*-dibenzo[c,h]chromene-2,8-diol (3.05 g, 8.89 mmol), tetramethyltin (2.39 g, 13.3 mmol), and dichlorobis(tri-*O*-tolylphosphine)palladium(II) (0.70 g, 0.9 mmol) in DMF (100 mL) were stirred at 80°C under nitrogen for 16 hours. The reaction was cooled to room temperature, poured into water (250 mL), and extracted with ethyl acetate (3x 250 mL). The combined organic layers were washed with ammonium chloride solution (50 mL), dried over sodium sulfate and filtered. Evaporation of the solvent and purification by silica column chromatography (40% ethyl acetate – hexanes) yielded 2.28 g (92%) of a light brown solid. A sample was further purified by reverse phase preparative HPLC to yield the title compound as an off white solid: mp 220-224 °C (d); ¹H NMR (Acetone-d₆): δ 2.56 (3H, s), 5.20 (2H, s), 6.78 (1H, d, *J* = 2.74 Hz), 6.89 (1H, dd, *J* = 2.74 Hz, *J* = 8.24 Hz), 7.12 (1H, dd, *J* = 2.47 Hz, *J* = 9.06 Hz), 7.25 (1H, d, *J* = 2.20 Hz), 7.64 – 7.66 (2H, m), 8.09 (1H, d, *J* = 8.79 Hz), 8.46 (1H, s), 8.60 (1H, s); MS (ESI) *m/z* 279 ([M+H]⁺); MS (ESI) *m/z* 277 ([M-H]⁻);

Anal. for C₁₈H₁₄O₃ · 0.30 H₂O:

Calc'd: C: 76.20 H: 5.19

Found: C: 75.90 H: 4.75

Example 1o**12-Vinyl-6*H*-dibenzo[*c,h*]chromene-2,8-diol**

To a mixture of 12-bromo-*H*-dibenzo[*c,h*]chromene-2,8-diol (0.63 g, 1.84 mmol) and dichlorobis(tri-*o*-tolylphosphine)palladium(II) (0.07 g, 0.09 mmol) in diethoxyethane (10 mL) was added tributylvinyltin (0.87 g, 2.76 mmol). The mixture was stirred for 12 hours at 110°C. The reaction was cooled to room temperature, poured into ammonium chloride solution (100 mL of 1 N) and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed with ammonium chloride solution (100 mL), dried over sodium sulfate and filtered. Evaporation of the solvent, and purification by silica column chromatography (30% ethyl acetate – hexanes) yielded 0.40 g (75%) of the title compound as a light yellow solid:

mp > 220 °C; ¹H NMR (DMSO-*d*₆): δ 5.20 (2H, s), 5.40 (1H, dd, *J* = 1.65 Hz, *J* = 10.99 Hz), 5.87 (1H, dd, *J* = 1.65 Hz, *J* = 17.58 Hz), 6.71 (1H, d, *J* = 2.75 Hz), 6.81 (1H, dd, *J* = 2.47 Hz, *J* = 8.51 Hz), 7.08 (1H, dd, *J* = 2.47 Hz, *J* = 9.06 Hz), 7.26 – 7.31 (2H, m), 7.72 (1H, d, *J* = 8.79 Hz), 7.94 (1H, s), 8.01 (1H, d, *J* = 9.34 Hz), 9.63 (1H, s), 9.85 (1H, s); MS (ESI) *m/z* 291 ([*M*+*H*]⁺); MS (ESI) *m/z* 289 ([*M*-*H*]⁻);

Anal. for C₁₉H₁₄O₃ · 0.25 H₂O:

Calc'd: C: 77.41 H: 4.96

Found: C: 77.34 H: 4.77

Example 1p**12-Ethyl-6*H*-dibenzo[*c,h*]chromene-2,8-diol**

To a solution of 12-vinyl-*H*-dibenzo[*c,h*]chromene-2,8-diol (0.19 g, 0.66 mmol) in ethyl acetate (30 mL) was added palladium on charcoal (0.23 g). The flask was fitted with a balloon filled with hydrogen and the suspension was stirred at room temperature for 4 hours. The reaction was filtered through Celite and purified by silica column chromatography (40 % ethyl acetate – hexanes) to yield 0.11 g (58 %) of a light brown solid which was further purified by reverse phase preparative HPLC to yield the title compound as a light purple solid: mp 184-192°C; ¹H NMR (DMSO-*d*₆): δ 1.31 (3H, t, *J* = 7.48 Hz), 2.89 – 2.95 (2H, m), 5.16 (2H, s), 6.69 (1H, d, *J* = 2.55 Hz), 6.80 (1H, dd, *J* = 2.49 Hz, *J* = 8.40 Hz), 7.04 (1H, dd, *J* = 2.32 Hz, *J* = 9.04 Hz), 7.20

(1H, d, $J = 2.21$ Hz), 7.61 – 7.63 (2H, m), 8.00 (1H, d, $J = 9.04$ Hz), 9.58 (1H, s), 9.74 (1H, s); MS (ESI) m/z 291 ([M-H]⁻);

Anal. for C₁₉H₁₆O₃ · 0.10 H₂O:

Calc'd: C: 77.59 H: 5.55

5 Found: C: 77.37 H: 5.58

Example 1q

12-Thien-3-yl--6H-dibenzo[c,h]chromene-2,8-diol

Method G

10 A mixture of 12-bromo-*H*-dibenzo[c,h]chromene-2,8-diol (0.51 g, 1.49 mmol), 3-thiophene boronic acid (0.38 g, 3 mmol), tetrakis(triphenylphosphine) palladium (0.17 g, 0.15 mmol), sodium carbonate solution (1.5 mL of 2 N), water (1 mL, and DME (5 mL) was stirred overnight at 85°C. The reaction was cooled to room temperature, poured into water (100 mL), and extracted into ethyl acetate (3-x 200
15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and filtered. Evaporation of the solvent and purification on silica (40% ethyl acetate – hexanes) yielded 0.43 g (84%) of a tan solid. This material was further purified by reverse phase preparative HPLC to yield the title compound as a tan solid: mp 179-
182 °C; ¹H NMR (DMSO-d₆): δ 5.23 (2H, s), 6.72 (1H, d, $J = 2.38$ Hz), 6.78 (1H, dd, $J = 2.38$ Hz, $J = 8.33$ Hz), 7.06 (1H, dd, $J = 2.38$ Hz, $J = 8.92$ Hz), 7.21 (1H, d, $J = 2.38$ Hz), 7.63 – 7.67 (2H, m), 7.72 – 7.73 (2H, m), 8.05 (1H, d, $J = 8.93$ Hz), 9.63 (1H, s), 9.75 (1H, s); MS (ESI) m/z 345 ([M-H]⁻);

Anal. for C₂₁H₁₄O₃S · 0.25 C₂H₃N · 0.50 H₂O:

Calc'd: C: 70.62 H: 4.34 N: 0.96

25 Found: C: 70.34 H: 4.41 N: 1.39.

Intermediate 26

12-Thien-2-yl-2,8-dimethoxy-6H-dibenzo[c,h]chromene

30 A mixture of 12-bromo-2,8-dimethoxy-*H*-dibenzo[c,h]chromene (0.53 g, 1.43 mmol), 2-thiophene boronic acid (0.2 g, 1.57 mmol), tetrakis(triphenylphosphine) palladium (0.08 g, 0.07 mmol), sodium carbonate solution (2 mL of 2 N), water (1 mL, and DME, 20 mL) was reacted overnight at 85 °C according to method G to yield 0.48 g (90 %) of a tan solid: mp 110-112°C; ¹H NMR (DMSO-d₆): δ 3.80 (3H, s), 3.81 (3H,

s), 5.33 (2H, s), 6.95-6.99 (2H, m), 7.22-7.27 (2H, m), 7.39-7.40 (1H, m), 7.48 (1H, d, $J=2.44$ Hz), 7.70 (1H, dd, $J=0.98, 5.37$ Hz), 7.76 (1H, d, $J=8.3$ Hz), 7.92 (1H, s), 8.16 (1H, d, $J=9.28$ Hz); MS (ESI) m/z 345 ([M-H]⁻)

Anal. for C₂₃H₁₈O₃S :

5 Calc'd: C: 73.77 H: 4.85

Found: C: 74.43 H: 4.78

Example 1r

12-Thien-2-yl-6H-dibenzo[c,h]chromene-2,8-diol

10 The title compound was prepared by reacting intermediate **26** and pyridinium HCl (2.85 g) according to Method D to afford 0.3 g (88%) of a light greenish yellow solid: mp 191-193°C; ; ¹H NMR (DMSO-d₆): δ 5.25 (2H, s), 6.72 (1H, d, $J=2.75$ Hz), 6.80 (1H, dd, $J=2.75, 8.24$ Hz), 7.90 (1H, dd, $J=2.20, 9.06$ Hz), 7.24-7.29 (2H, m), 7.37 (1H, d, $J=2.20$ Hz), 7.65-7.68 (2H, m), 7.79 (1H, s), 8.07 (1H, d, $J=8.79$ Hz), 9.66
15 (1H, bs), 9.85 (1H, bs); HRMS calc'd for C₂₃H₁₈O₃S+H (M+1) 375.10495 observed 375.10497.

Anal. for C₂₁H₁₄O₃S·0.65 H₂O :

Calc'd: C: 70.43 H: 4.30

Found: C: 70.02 H: 3.85

20

Example 1s

12-Butyl-6H-dibenzo[c,h]chromene-2,8-diol

The title compound was prepared by reacting 12-bromo-*H*-dibenzo[c,h]-chromene-2,8-diol (1.07 g, 3.12 mmol) with butyl boronic acid (0.46 g, 4.55 mmol)
25 according to method G to yield 0.12 g (12%) of a light yellow solid which was further purified by reverse phase preparative HPLC to yield a light purple solid: mp 118-121°C; ¹H NMR (DMSO-d₆): δ 0.96 (3H, t, $J = 7.30$ Hz), 1.38 – 1.47 (2H, m), 1.62 – 1.69 (2H, m), 2.90 (2H, t, $J = 7.59$ Hz), 5.16 (2H, s), 6.69 (1H, d, $J = 2.09$ Hz), 6.80 (1H, dd, $J = 2.38$ Hz, $J = 8.39$ Hz), 7.04 (1H, dd, $J = 2.20$ Hz, $J = 9.04$ Hz), 7.20 (1H,
30 d, $J = 2.09$ Hz), 7.60 – 7.62 (2H, m), 7.99 (1H, d, $J = 9.04$ Hz), 9.58 (1H, s), 9.73 (1H, s); MS (ESI) m/z 321 ([M+H]⁺); MS (ESI) m/z 319 ([M-H]⁻);

Anal. for C₂₁H₂₀O₃ · 0.10 H₂O:

Calc'd: C: 78.29 H: 6.32

Found: C: 78.13 H: 6.30

Intermediate 27**8-Dimethoxy-12-propenyl-6H-dibenzo[c,h]chromene**

A mixture of 12-bromo-2,8-dimethoxy-6H-dibenzo[c,h]chromene (1.4 g, 3.78 mmol) allyltributyltin (1.76 ml, 5.68 mmols) and dichlorobis(triphenylphosphine) palladium (II) (133 mg, 0.19 mmols) in m-xylene (38 ml) was heated at 130°C with stirring for 1h. TLC and LC-MS indicated that the reaction was not complete. The mixture was filtered through celite and fresh dichlorobis(triphenylphosphine) palladium (II) (133 mg, 0.19 mmols) catalyst was added into the reaction and the mixture heated at 130°C for 2h. TLC and LC-MS indicated that the reaction was still not complete. Therefore, filtration and addition of fresh catalyst was repeated two more times. The mixture was filtered through celite, stripped of solvent and purified by silica chromatography (20% - 40% dichloromethane - hexane) to yield 0.84 g (67%) of the title compound as a yellowish solid: ¹H NMR (DMSO-d₆): δ 2.02 (3H, dd, *J* = 6.57 Hz, *J* = 1.73 Hz), 3.86 (3H, s), 3.96 (3H, s), 5.24 (2H, s), 6.17-6.18 (1H, m), 6.75 (1H, d, *J* = 2.52 Hz), 6.94 (1H, dd, *J* = 8.57 Hz, *J* = 2.61 Hz), 7.01 (1H, *J* = 15.43 Hz, *J* = 1.54 Hz), 7.14 (1H, dd, *J* = 9.14 Hz, *J* = 2.52 Hz), 7.31 (1H, d, *J* = 2.44 Hz), 7.69 (1H, d, *J* = 8.57 Hz), 7.81 (1H, s), 8.17 (1H, d, *J* = 9.16 Hz); MS (ESI) *m/z* 333 (M+H)⁺.

Intermediate 28**2,8-Dimethoxy-12-propyl-6H-dibenzo[c,h]chromene**

A mixture of 2,8-dimethoxy-12-propenyl-6H-dibenzo[c,h]chromene (460 mg, 1.38 mmols) and palladium (92 mg, 10% on activated carbon) in 36 ml ethyl acetate was stirred under a hydrogen balloon at room temperature for 3 hours. The reaction mixture was filtered through Celite and concentrated to give 430 mg (94 %) of the title compound as a light brown solid. The analytical sample was obtained by further purification with reverse-phase preparative HPLC: mp 88-90 °C; ¹H NMR (DMSO-d₆): δ 1.01 (3H, t, *J* = 7.31 Hz), 1.68-1.80 (2H, m), 2.98 (2H, t, *J* = 7.29 Hz), 3.81 (3H, s), 3.91 (3H, s), 5.25 (2H, s), 6.93 (1H, d, *J* = 2.53 Hz), 6.98 (1H, dd, *J* = 8.46 Hz, *J* = 2.04 Hz), 7.17 (1H, dd, *J* = 9.20 Hz, *J* = 2.38 Hz), 7.28 (1H, d, *J* = 2.36 Hz), 7.72 (1H, s), 7.77 (1H, d, 8.57 Hz), 8.08 (1H, d, *J* = 9.14 Hz); MS (ESI) *m/z* 335 (M+H)⁺.

Anal. for C₂₂H₂₂O₃:

Calc'd: C: 79.02 H: 6.63

Found: C: 78.48 H: 6.75

Example 1t**12-Propyl-6H-dibenzo[c,h]chromene-2,8-diol**

To a mixture of 2,8-dimethoxy-12-propyl-6H-dibenzo[c,h]chromene (220 mg, 0.658 mmols) in CH₂Cl₂ (33 ml) at 0 ° C was slowly added boron tribromide (3.95 ml of 1N solution in CH₂Cl₂, 3.95 mmols). The reaction mixture was stirred at 0 ° C for 3h. 4 ml water was injected into the mixture with stirring in an ice-water bath. CH₂Cl₂ in the mixture was removed under reduced pressure. The resulting mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and stripped of solvent to give 120 mg (60 %) of the title compound as white solid. The analytical sample was obtained by purification with silica column chromatography (20%-30% ethyl acetate - hexane) and then recrystallization with ethyl acetate - hexane: mp 86-95°C; ¹H NMR (DMSO-d₆): δ 1.00 (3H, t, *J* = 7.24 Hz), 1.63-1.76 (2H, m), 2.87 (2H, t, *J* = 7.22 Hz), 5.16 (2H, s), 6.69 (1H, d, *J* = 2.28 Hz), 6.79 (1H, dd, *J* = 8.39 Hz, *J* = 2.28 Hz), 7.03 (1H, dd, *J* = 9.02 Hz, *J* = 2.18 Hz), 7.20 (1H, d, *J* = 2.10 Hz), 7.60 (1H, s), 7.62 (1H, d, *J* = 7.85 Hz), 7.99 (1H, d, *J* = 9.01 Hz), 9.61 (1H, s), 7.76 (1H, s); MS (ESI) *m/z* 305 (M-H)⁻, 307 (M+H)⁺; HRMS: calcd for C₂₀H₁₈O₃, 306.1256; found (ESI), 305.11827.

Anal. for C₂₀H₁₈O₃:
Calc'd: C: 78.41 H: 5.92
Found: C: 72.79 H: 6.62

Intermediate 30**5-Methoxy-1-naphthol**

In a 2000 ml flask a mixture of 5-methoxy-1-tetralone (30.0 g, 170.2 mmol) and 10% Pd/C (40 g) in 1000 ml p-cymene was brought to reflux and monitored by LC-MS until no more starting material was present (approx. 24 h). The mixture was then cooled to room temperature and passed through a silica gel/celite plug and concentrated under vacuum to 26.6 g (90 %) of an off-white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 3.90 (3H, s), 6.83 (1H, appd, *J* = 7.5 Hz), 6.89 (1H, appd, *J* = 7.7 Hz), 7.24 (1H, appt), 7.30 (1H, appt), 7.54 (1H, appd, *J* = 8.5 Hz), 7.65 (1H, d, *J* = 8.5 Hz), 9.98 (1H, s).

Intermediate 31**1-[(2-bromo-5-methoxybenzyl)oxy]-5-methoxynaphthalene**

To a mixture of 5-methoxy-1-naphthol (26.0 g, 149 mmol), triphenylphosphine (43.3 g, 165 mmol), (2-bromo-5-methoxyphenyl)methanol (36.0 g, 166 mmol), and THF (500 ml) was added DEAD (28.7 g in 50 ml THF, 165 mmol) dropwise. The reaction was then stirred overnight, concentrated, dissolved in a minimum amount of ether, and cooled at approx. -30°C to form a white precipitate (PPh_3O and reduced DEAD) which was filtered off. The filtrate was concentrated and dissolved in a minimum amount of dichloromethane and cooled to -30°C . The precipitate was filtered off on a silica plug and the filtrate was concentrated to 28.7 g (51.5 %) of white solid. mp $120-121^{\circ}\text{C}$; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.77 (3H, s), 3.96 (3H, s), 5.26 (2H, s), 6.94 (1H, dd, $J = 8.8$ Hz, 3.1 Hz), 7.01 (1H, d, $J = 7.6$ Hz), 7.11 (1H, d, $J = 7.6$ Hz), 7.28 (1H, d, $J = 3.1$ Hz), 7.42 (2H, m), 7.61 (1H, d, $J = 8.8$ Hz), 7.75 (2H, appd); MS m/z 373/275 (Br pattern) ($\text{M} + \text{H}^+$).

Anal. for $\text{C}_{19}\text{H}_{17}\text{BrO}_3$:

Calc'd: C: 61.14 H: 4.59

Found: C: 60.86 H: 4.42

Intermediate 32**1,8-Dimethoxy-6H-dibenzo[c,h]chromene**

To a 2000 ml recovery flask was added 1-[(2-bromo-5-methoxybenzyl)oxy]-5-methoxynaphthalene (3.0 g, 8.03 mmol), potassium acetate (2.4 g anhyd., 24.10 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (1.12 g, 1.60 mmol), and N,N -dimethylacetamide (500 ml 99%). The flask was purged with nitrogen, heated to 130°C for 12 h, and concentrated under high vacuum. The dark solids were then dissolved in ether/ CH_2Cl_2 (1/1 300 ml) and passed through a silica gel/celite plug. Evaporation under reduced pressure afforded 2.32 g (99%) product as a tan colored solid. mp $166-167^{\circ}\text{C}$; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.82 (3H, s), 3.97 (3H, s), 5.30 (2H, s), 6.98 (3H, m), 7.42 (1H, t, $J = 8.1$ Hz), 7.69 (1H, d, $J = 8.5$ Hz), 7.81 (2H, appd, $J = 8.6$ Hz), 7.91 (1H, d, $J = 8.9$ Hz); MS m/z 293 ($\text{M} + \text{H}^+$).

Anal. for $\text{C}_{19}\text{H}_{16}\text{O}_3$:

Calc'd: C: 78.06 H: 5.52

Found: C: 77.67 H: 5.28

Example 1u**6H-dibenzo[c,h]chromene-1,8-diol**

The title compound was prepared by reacting 1,8-dimethoxy-6H dibenzo[c,h]-
5 chromene (1.0 g, 3.42 mmol) with pyridine hydrochloride (5.0g, 43.3 mmol) according
to method D to yield 0.93 g (99 %) white foam. mp 213-214°C; ¹H NMR (300 MHz,
DMSO-d₆) δ 5.21 (2H, s), 6.72 (1H, d, *J* = 1.9 Hz), 6.82 (2H, m), 7.27 (1H, t, *J* = 7.9
Hz), 7.54 (1H, d, *J* = 8.3 Hz), 7.68 (1H, d, *J* = 8.4 Hz), 7.78 (2H, brs), 9.72 (1H, s),
10.09 (1H, s); MS *m/z* 263 (*M* – H⁺);

10 Anal. for C₁₇H₁₂O₃:

Calc'd: C: 77.26 H: 4.58

Found: C: 76.62 H: 4.42

Intermediate 33**1-(Acetyloxy)-6H-dibenzo[c,h]chromen-8-yl acetate**

The title compound was prepared by reacting 6H-dibenzo[c,h]chromene-1,8-
diol (1.5 g, 5.68 mmol), acetic anhydride (25 ml), and pyridine (25 ml) according to
method E to produce 1.88 g (95%) of product as a white solid. mp 142-143°C; ¹H
NMR (300 MHz, DMSO-d₆) δ 2.31 (3H, s), 2.47 (3H, s), 5.38 (2H, s), 7.18 (1H, d, *J* =
20 2.0 Hz), 7.22 (1H, dd, *J* = 8.4 Hz, 2.3 Hz), 7.33 (1H, d, *J* = 7.1 Hz), 7.55 (1H, t, *J* = 8.0
Hz), 7.60 (1H, d, *J* = 8.9 Hz), 7.95 (1H, d, *J* = 8.4 Hz), 8.06 (2H, appt);
MS *m/z* 349 (*M* + H⁺);

Anal. for C₂₁H₁₆O₅:

Calc'd: C: 72.41 H: 4.63

25 Found: C: 72.06 H: 4.72

Example 1v**12-Chloro-6H-dibenzo[c,h]chromene-1,8-diol**

The title compound was prepared by reacting 1-(Acetyloxy)-6H-dibenzo[c,h]-
30 chromen-8-yl acetate (360 mg, 1.03 mmol) with NCS (210 mg, 1.57 mmol) and
anhydrous DMF (20 ml) according to method B for 2.0 h at room temperature,
followed by heating to 100°C for 1 h. The reaction was concentrated under reduced
pressure and the solids were dissolved in MeOH (30 ml). NH₃ was bubbled in for 0.5
h while acetate removal was monitored by LC-MS. The reaction was concentrated to

a dark sludge, dissolved in EtOAc and passed through a silica plug to produce 200 mg (65%) foam. An analytical sample was produced by silica chromatography (1:1 EtOAc:hexanes). mp ~185°C dec.; ¹H NMR (400 MHz, DMSO-d₆) δ 5.23 (2H, s), 6.72 (1H, d, *J* = 2.3 Hz), 6.81 (1H, dd, *J* = 8.6 Hz, 2.6 Hz), 6.92 (1H, dd, *J* = 7.5 Hz, 1.0 Hz), 7.33 (1H, appt), 7.62 (1H, dd, *J* = 8.5 Hz, 1.0 Hz), 7.69 (1H, d, *J* = 8.6 Hz), 7.79 (1H, s), 9.78 (1H, s), 10.11 (1H, s); MS *m/z* 297/399 (Cl pattern) (M - H⁺).

Anal. for C₁₇H₁₁ClO₃:

Calc'd: C: 68.35 H: 3.71

Found: C: 67.85 H: 3.61

10

Example 1w

12-Bromo-6H-dibenzo[c,h]chromene-1,8-diol

The title compound was prepared by reacting 1-(Acetyloxy)-6H-dibenzo[c,h]chromen-8-yl acetate (510 mg, 1.46 mmol), NBS (315 mg, 1.77 mmol), and anhydrous DMF (30 ml) at room temperature for 1.5 hours according to method B. The reaction was concentrated under reduced pressure, dissolved in MeOH (30 ml), and NH₃ was bubbled in for 1.5 h while acetate removal was monitored by LC-MS. The reaction was concentrated to a dark sludge and purified by silica chromatography (1:1 EtOAc:hexanes) to afford 340 mg (68%) of product as a tan solid. Mp: decomposes above 130°C; ¹H NMR (500 MHz, DMSO-d₆) δ 5.23 (2H, s), 6.72 (1H, d, *J* = 1.9 Hz), 6.81 (1H, dd, *J* = 8.2 Hz, 2.5 Hz), 6.92 (1H, dd, *J* = 7.7 Hz, 1.1 Hz), 7.33 (1H, t, *J* = 8.0 Hz), 7.64 (1H, dd, *J* = 8.5 Hz, 1.1 Hz), 7.68 (1H, d, *J* = 8.5 Hz), 8.01 (1H, s), 9.78 (1H, s), 10.15 (1H, s); MS *m/z* 341/343 (Br pattern) (M - H⁺).

Anal. for C₁₇H₁₁BrO₃:

Calc'd: C: 59.50 H: 3.23

Found: C: 59.23 H: 3.34

25

Example 1x

1,8-Dihydroxy-6H-dibenzo[c,h]chromene-12-carbonitrile

In a 10 ml flask was added bromide (165 mg, 0.48 mmol), Pd(PPh₃) (28 mg, 0.024 mmol), zinc cyanide (68 mg, 0.58 mmol), and DMF (5 ml). The mixture was heated to 120 °C for 12 h after which no reaction took place. Copper cyanide (43 mg, 0.48 mmol) was then added and the reaction was complete in 1 h by LC-MS. After the reaction cooled it was diluted with EtOAc, passed through a silica plug,

30

concentrated, and purified by preparative reverse-phase HPLC (water/CH₃CN 0.1 % TFA) and concentrated under reduced pressure to a white solid. The solids were dried in a drying pistol (100°C overnight) to produce 30 mg product (21%) as a white solid. mp dec. above 260°C; ¹H NMR (300 MHz, DMSO-d₆) δ 2.06 (2H, m), 2.60 (2H, t, *J* = 6.5 Hz), 2.99 (2H, t, *J* = 5.9 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 7.57 (4H, m), 7.86 (1H, d, *J* = 8.7 Hz), 9.74 (1H, s); MS *m/z* 237 (*M* – H⁺).

Anal. for C₁₆H₁₄O₂:

Calc'd: C: 80.65 H: 5.92

Found: C: 79.04 H: 5.60

10

Example 1y and Example 1z

2-Chloro-6H-dibenzo[c,h]chromene-1,8-diol (Ex. 1y) and

4-chloro-6H-dibenzo[c,h]chromene-1,8-diol (Ex. 1z)

The title compound was prepared by reacting 6H-dibenzo[c,h]chromene-1,8-diol (150 mg, 0.57 mmol), NCS (84 mg, 0.63 mmol), and THF (8 ml) for 3 h at r.t and for 5 h at 60°C according to method B. The reaction was purified by preparative HPLC to afford 35 mg 2-chloro compound and 10 mg 4-chloro compound (27% overall).

2-chloro compound: mp 181-182 °C dec.; ¹H NMR (300 MHz, DMSO-d₆) δ 5.24 (2H, s), 6.72 (1H, d, *J* = 2.3 Hz), 6.83 (1H, dd, *J* = 8.4 Hz, 2.4 Hz), 7.40 (1H, d, *J* = 9.0 Hz), 7.61 (1H, d, *J* = 9.0 Hz), 7.71 (1H, d, *J* = 8.5 Hz), 7.64 (1H, d, *J* = 8.9 Hz), 7.91 (1H, d, *J* = 9.0 Hz), 9.77 (1H, s), 10.01 (1H, s); HRMS Exact: 297.03239 (*M* – H⁺) Found: 297.03240 (0.02 ppm);

Anal. for C₁₇H₁₁ClO₃:

25 Calc'd: C: 68.35 H: 3.71

Found: C: 67.66 H: 3.68

4-chloro compound: mp; ¹H NMR (300 MHz, DMSO-d₆) δ 5.14 (2H, s), 6.73 (1H, d, *J* = 2.4 Hz), 6.77 (1H, d, *J* = 8.2 Hz), 6.84 (1H, dd, *J* = 8.5 Hz, 2.5 Hz), 7.31 (1H, d, *J* = 8.2 Hz), 7.70 (1H, d, *J* = 8.5 Hz), 7.87 (2H, appq), 9.78 (1H, s), 9.77 (1H, s), 10.40 (1H, s); HRMS Exact: 297.03239 (*M* – H⁺) Found: 297.03236 (-0.11 ppm)

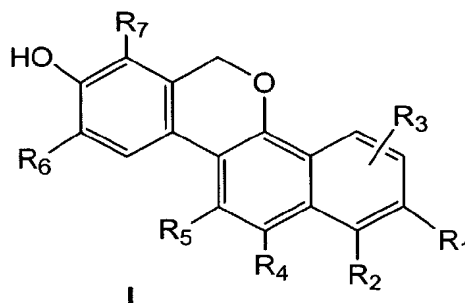
30 Anal. for C₁₇H₁₁ClO₃:

Calc'd: C: 68.35 H: 3.71

Found: C: 66.12 H: 3.57

CLAIMS

1. A compound of formula I having the structure



5 wherein

R₁ and R₂ are each, independently, selected from hydrogen, hydroxyl, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, or halogen; wherein the the alkyl or alkenyl moieties of R₁, or R₂ may be optionally substituted with hydroxyl, -CN, halogen, trifluoroalkyl, trifluoroalkoxy, -NO₂ or phenyl; and provided that at least one of R₁ or R₂ is hydroxyl;

R₃, R₄, R₅, R₆, and R₇ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, halogen, alkoxy of 1-6 carbon atoms, -CN, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, -CHO, phenyl, or a 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S; wherein the alkyl or alkenyl moieties of R₄, R₅, R₆ or R₇ may be optionally substituted with hydroxyl, -CN, halogen, trifluoroalkyl, trifluoroalkoxy, -NO₂ or phenyl; wherein the phenyl moiety of R₄ or R₅ may be optionally mono-, di-, or tri-substituted with a substituent, the same or different, selected from alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, halogen, hydroxyl, alkoxy of 1-6 carbon atoms, -CN, -NO₂, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl group, thio, alkylthio of 1-6 carbon atoms, alkylsulfinyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, alkoxycarbonyl of 2-7 carbon atoms, alkylcarbonyl of 2-7 carbon atoms, or benzoyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R_6 and R_7 are each, independently, hydrogen or halogen.
3. A compound according to claim 1 or claim 2 wherein R_6 is hydrogen or
5 fluorine.
4. A compound according to any one of claims 1 to 3 wherein R_4 and R_5 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, alkenyl of 2-7 carbon atoms, -CN, furyl, or thienyl.
10
5. A compound according to any one of claims 1 to 4 wherein R_4 is not hydrogen.
6. A compound according to claim 5 wherein R_4 is selected from cyano, chloro, bromo, methyl, ethyl, propyl, butyl, methoxy, vinyl, thien-2-yl and thien-3-yl.
15
7. A compound according to any one of claims 1 to 6 wherein R_5 is hydrogen or halogen.
8. A compound according to any one of claims 1 to 7 wherein R_2 , and R_3 are
20 each, independently, hydrogen, halogen, or hydroxyl.
9. A compound according to any one of claims 1 to 8 wherein R_2 is hydroxyl or halogen.
- 25 10. A compound according to any one of claims 1 to 8 wherein R_2 is hydroxy.
11. A compound according to any one of claims 1 to 10 wherein R_3 is hydrogen or halogen.
- 30 12. A compound according to any one of claims 1 to 11 wherein R_1 is hydrogen, hydroxyl or halogen.

13. A compound according to claim 1, which is one of the following:
- a) 6*H*-Dibenzo[*c,h*]chromene-2,8-diol;
 - b) 9-Fluoro-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - c) 2,8-Dihydroxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile;
 - 5 d) 9-fluoro-2,8-dihydroxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile;
 - e) 1-Chloro-2,8-dihydroxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile;
 - f) 1-Chloro-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - g) 12-Bromo-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - h) 12-Chloro-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - 10 i) 12-Bromo-9-fluoro-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - j) 12-Chloro-9-fluoro-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - k) 12-Methoxy-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - l) 11-Chloro-12-methoxy-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - m) 12-Methyl-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - 15 n) 12-Vinyl-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - o) 12-Ethyl-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - p) 12-Thien-3-yl--6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - q) 12-Thien-2-yl-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - r) 12-Butyl-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - 20 s) 12-Propyl-6*H*-dibenzo[*c,h*]chromene-2,8-diol;
 - t) 6*H*-dibenzo[*c,h*]chromene-1,8-diol;
 - u) 12-Chloro-6*H*-dibenzo[*c,h*]chromene-1,8-diol;
 - v) 12-Bromo-6*H*-dibenzo[*c,h*]chromene-1,8-diol;
 - w) 1,8-Dihydroxy-6*H*-dibenzo[*c,h*]chromene-12-carbonitrile;
 - 25 x) 2-Chloro-6*H*-dibenzo[*c,h*]chromene-1,8-diol;
 - y) 4-chloro-6*H*-dibenzo[*c,h*]chromene-1,8-diol;

or a pharmaceutically acceptable salt thereof.

14. A compound which is 6*H*-Dibenzo[*c,h*]chromen-8-ol or a pharmaceutically
30 acceptable salt thereof.

15. A method of treating or inhibiting prostatitis or interstitial cystitis in a mammal
in need thereof, which comprises providing to said mammal an effective amount of a

compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

16. A method of treating or inhibiting inflammatory bowel disease, Crohn's
5 disease, ulcerative proctitis, or colitis in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

17. A method of treating or inhibiting prostatic hypertrophy, uterine leiomyomas,
10 breast cancer, endometrial cancer, polycystic ovary syndrome, endometrial polyps, benign breast disease, adenomyosis, ovarian cancer, melanoma, prostate cancer, colon cancer, glioma or astioblastoma in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

18. A method of lowering cholesterol, triglycerides, Lp(a), or LDL levels; inhibiting
15 or treating hypercholesteremia; hyperlipidemia; cardiovascular disease; atherosclerosis; hypertension; peripheral vascular disease; restenosis, or vasospasm; or inhibiting vascular wall damage from cellular events leading toward immune
20 mediated vascular damage in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

19. A method of providing cognition enhancement or neuroprotection; or treating
25 or inhibiting senile dementias, Alzheimer's disease, cognitive decline, stroke, anxiety, or neurodegenerative disorders in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

20. A method of treating or inhibiting free radical induced disease states in a
30 mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

21. A method of treating or inhibiting vaginal or vulvar atrophy; atrophic vaginitis; vaginal dryness; pruritus; dyspareunia; dysuria; frequent urination; urinary incontinence; urinary tract infections in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed
5 in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.
22. A method of treating or inhibiting vasomotor symptoms in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I, as claimed in any one of claims 1 to 14 or a pharmaceutically
10 acceptable salt thereof.
23. A method of inhibiting conception in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.
15
24. A method of treating or inhibiting arthritis in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.
- 20 25. A method according to claim 24, wherein the arthritis is rheumatoid arthritis, osteoarthritis, or spondyloarthropathies.
26. A method of treating or inhibiting joint swelling or erosion; or treating or inhibiting joint damage secondary to arthroscopic or surgical procedures in a mammal
25 in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.
27. A method of treating or inhibiting psoriasis or dermatitis in a mammal in need
30 thereof, which comprises providing to said mammal an effective amount of a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

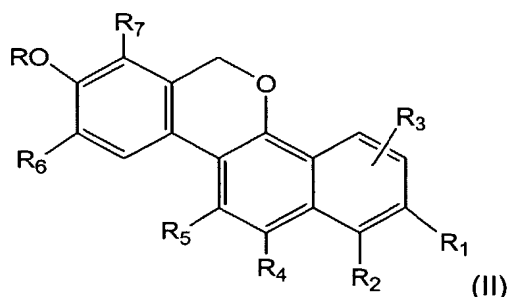
28. A method of treating or inhibiting ischemia, reperfusion injury, asthma, pleurisy, multiple sclerosis, systemic lupus erythematosus, uveitis, sepsis, hemorrhagic shock, macular degeneration or type II diabetes in a mammal in need thereof, which comprises providing to said mammal an effective amount of a
5 compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

29. A method of treating or inhibiting endometriosis in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of
10 formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

30. A pharmaceutical composition which comprises a compound of formula I as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof,
15 and a pharmaceutical carrier.

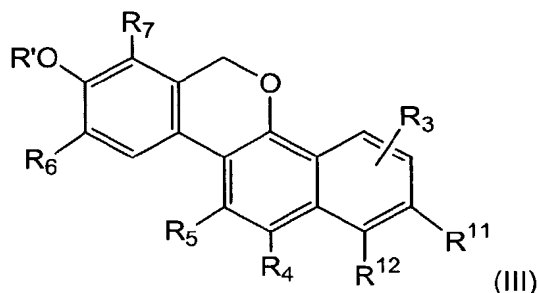
31. A process for preparing a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, which comprises one of the following:

20 a) de-alkylating a compound of formula II:



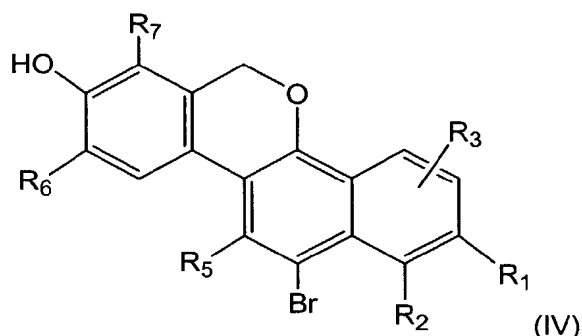
wherein R is an alkyl group of 1 to 6 carbon atoms and R₁, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined in claim 1, to give a compound of formula I; or

b) de-acylating a compound of formula III:



wherein R' is an acyl group, e.g., alkanoyl of 2-7 carbon atoms such as acetyl, R^{11} is R_1 or an acyloxy group, e.g., alkanoyl of 2-7 carbon atoms such as acetyl, R^{12} is R_2 or an acyloxy group, e.g., alkanoyl of 2-7 carbon atoms such as acetyl, and R_3 , R_4 , R_5 , R_6 , R_7 , are as defined in claim 1, to give a compound of formula I; or

c) reacting a 12- bromo compound of formula IV:

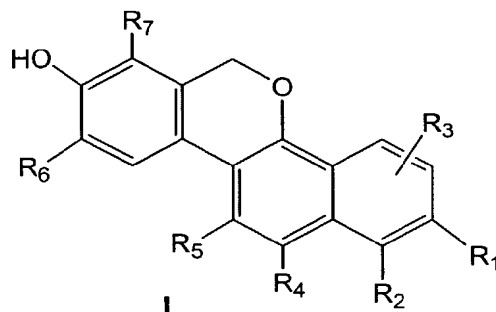


protected as necessary, wherein R_1 , R_2 , R_3 , R_5 , R_6 and R_7 are as defined in claim 1, with a reactive derivative of formula



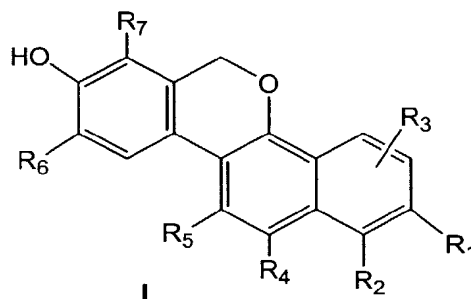
e.g., where L is a boronic acid or butyltin derivative and R_4 is alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 7 carbon atoms or a 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S; and removing any protecting groups to give a corresponding compound of formula (I); or

d) halogenating a compound of formula I:



as defined in claim 1 protected if necessary, and wherein at least one of R₁, R₂, R₃, R₄ and R₅ is hydrogen, with a halogenating agent followed if necessary by deprotection, to give a compound of formula I wherein at least one of R₁, R₂, R₃ and R₄ is halogen; or

e) nitrilating a compound of formula I:



as defined in claim 1 protected as necessary, and wherein R₄ is bromine, with a nitrilating agent, e.g., zinc cyanide, followed if necessary by deprotection, to give a compound of formula I wherein R₄ is cyano; or

f) converting a basic compound of formula I to a pharmaceutically acceptable salt thereof or vice versa.

INTERNATIONAL SEARCH REPORT

Initial Application No

PCT/US 02/39802

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D311/02 C07D409/04 A61K31/352 A61K31/381 A61P5/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SATHYAMOORTHY N ET AL: "Differential effects of dietary phyto-oestrogens daidzein and equol on human breast cancer MCF-7 cells" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 33, no. 14, December 1997 (1997-12), pages 2384-2389, XP004284600 ISSN: 0959-8049 Page 2385, figure 1: Equol. ---	1-31
A	US 5 696 127 A (ZHI LIN ET AL) 9 December 1997 (1997-12-09) Abstract; column 1, lines 12-17; claim 1. --- -/--	1-31



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 March 2003

Date of mailing of the international search report

18/03/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Weisbrod, T

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/39802

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LLOYD D G ET AL: "RECENT ADVANCES IN ESTROGEN RECEPTOR ANTAGONISTS" IDRUGS, CURRENT DRUGS LTD, GB, vol. 3, no. 6, 2000, pages 632-642, XP008008750 ISSN: 1369-7056 the whole document -----	1-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/39802

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 23 is directed to a method for inhibiting contraception, and the claims 15-22 and 24-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JS 02/39802

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